0.4.治療

A 群:GEM+CDDP 併用(GC)療法

GEM:1 回量 1,000 mg/m^{2}を day 1 と day 8 に 30 分間の点滴静注

CDDP:25 mg/m^{2}を day 1 と day 8 に 60 分間の点滴静注

3 週(21 日)を 1 コースとして、プロトコール治療中止規準に該当するまで投与を繰り返す。

※GC 療法としては、CDDP 最大 16 回投与まで。CDDP 中止規準に該当後は GEM 単剤療法を継続する。

投与スケジュール

CDDP:16 回投与まで

	投与量	day 1	day 8	day 15	day 22(次コース day 1)
GEM	1,000 mg/m^2/day	↓	↓		↓
CDDP	25 mg/m^2/day	↓	↓		↓

CDDP:16 回投与後

GEM のみを 4 週(28 日)を 1 コースとして、プロトコール治療中止規準に該当するまで投与を繰り返す。

	投与量	day 1	day 8	day 15	day 22	day 29(次コース day 1)
GEM	1,000 mg/m^2/day	↓	↓	↓		↓

B 群:GEM+S-1 併用(GS)療法

GEM:1 回量 1,000 mg/m^{2}を day 1 と day 8 に 30 分間の点滴静注

S-1:体表面積に合わせた投与量(60 mg、80 mg、100 mg/日)を朝夕食後の 1 日 2 回に分け、14 日間連日経口投与し、その後 7 日間休薬する。

3 週(21 日)を 1 コースとして、プロトコール治療中止規準に該当するまで投与を繰り返す。

投与スケジュール

	投与量	day 1	day 8	day 15	day 22(次コース day 1)
GEM	1,000 mg/m^2/day	↓	↓		↓
S-1	60-100 mg/m^2/day	←――――――→ (day1～14)			←――

0.5.予定登録数と研究期間

予定登録患者数:各群 175 名　合計 350 名。

登録期間:4 年。追跡期間:登録終了後 1 年。総研究期間:5 年

ただし 6 か月以内の登録期間の延長は、プロトコール改訂手続き不要とする。

0.6.　問い合わせ先

適格規準、治療変更規準など、臨床的判断を要するもの:研究事務局(表紙、16.6.)

登録手順、記録用紙(CRF)記入など:JCOG データセンター(16.11.)

有害事象報告:JCOG 効果・安全性評価委員会事務局(16.9.)

JCOG
Japan Clinical Oncology Group

Japan Clinical Oncology Group（日本臨床腫瘍研究グループ）
肝胆膵グループ

独立行政法人国立がん研究センターがん研究開発費 23-A-22
「難治性悪性腫瘍に対する標準治療確立のための多施設共同研究」班

JCOG1202

根治切除後胆道癌に対する術後補助療法としての S-1 療法の第 III 相試験 実施計画書 ver1.1

A phase III trial of S-1 vs. observation in patients with resected biliary tract cancer

ASCOT: Adjuvant S-1 for CholangiOcarcinoma Trial

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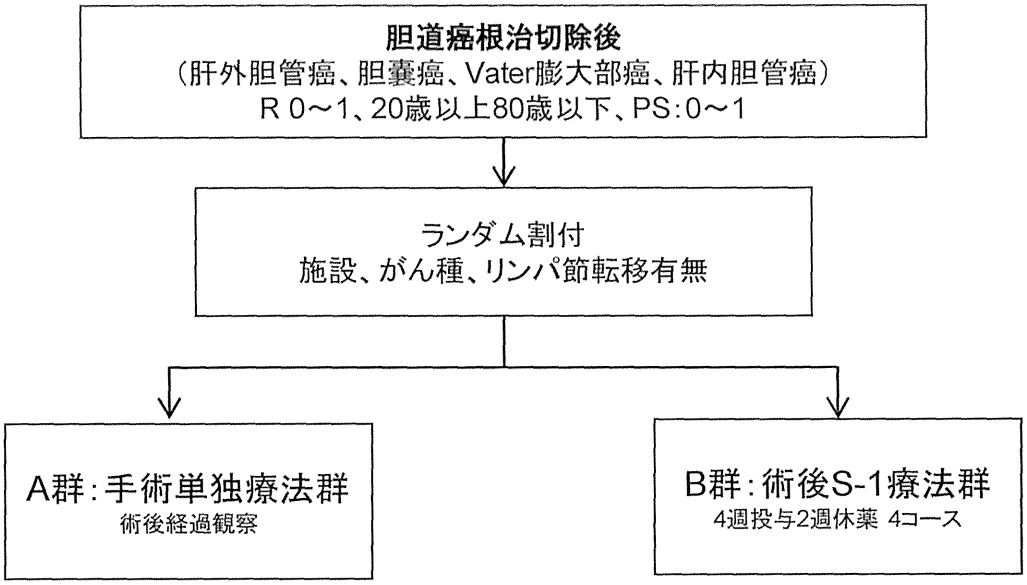
2012 年 6 月 23 日 JCOG 運営委員会プロトコールコンセプト承認（PC1202）
2013 年 7 月 29 日 JCOG プロトコール審査委員会審査承認
2013 年 12 月 5 日 ver1.1 改訂 JCOG 効果・安全性評価委員会承認 12 月 6 日発効

0. 概要

0.1. シェーマ



0.2. 目的

胆道癌(肝外胆管癌、胆嚢癌、Vater 膨大部癌、肝内胆管癌)根治切除患者を対象として、術後 S-1 療法が、手術単独療法に対して優れていることをランダム化比較試験にて検証する。

Primary endpoint	全生存期間(Overall survival)
Secondary endpoints	無再発生存期間(Relapse free survival)、有害事象発生割合、治療完遂割合、重篤な有害事象(有害反応)発生割合

0.3. 対象

1) 術後の最終病理診断で腺癌(乳頭腺癌、管状腺癌)、腺扁平上皮癌であることが確認されている、肝外胆管癌、胆嚢癌、Vater 膨大部癌、肝内胆管癌である。
2) 術後の病理診断が、UICC 病期分類(第 7 版)にて以下を満たす。
   肝外胆管癌(肝門部)、肝外胆管癌(遠位部)、胆嚢癌、Vater 膨大部癌:
   T2-4、N0、M0 または T1-4、N1、M0
   肝内胆管癌:T1-4、N0-1、M0
   ※がん種が重複している場合は、最も進行度が進んだがん種の病期で適格性を判定する。
3) 遺残腫瘍(R)分類が R0 または R1 である。
4) 登録時の年齢が 20 歳以上、80 歳以下。
5) Performance status (PS)は ECOG の規準で 0 または 1 である。
6) 術後登録前の CT もしくは MRI にて、遠隔転移がなく、かつ中等量以上の胸水・腹水がない※。
   ※中等量以上の腹水とは、骨盤腔を越える場合を目安とし、中等量以上の胸水とは立位単純胸部 X 線における胸水量が左右いずれかの肺野の 3 分の 1 を越える場合を目安とする。
7) 原発巣に対して手術が行われており、かつ肝外胆管癌、胆嚢癌、Vater 膨大部癌、肝門部進展を伴う肝内胆管癌においては D1 以上のリンパ節郭清が行われている。肝門部進展を伴わない肝内胆管癌においてはリンパ節郭清の有無は問わない。
8) 他のがん種に対する治療も含めて化学療法、放射線治療、いずれの既往もない。
9) 術後 2 週(14 日)以上 10 週(70 日)以内である。
10) 十分な経口摂取が可能である。
11) 手術創が閉鎖しており、ドレーンが抜去されている。
12) 水様性の下痢がない。

13) 臓器機能が保たれている。
14) 試験参加について患者本人から文書で同意が得られている

0.4. 治療

A 群:手術単独療法

再発が確認されるまではあらゆる抗がん治療は行わない。

B 群:術後 S-1 療法

S-1:朝夕食後の 1 日 2 回、28 日間(56 回)連日経口投与し、その後 14 日間休薬する。(1 コース)
4 コースまで施行する。

薬剤	投与量	投与法	投与日	休薬日
S-1	80～120 mg/body/日	1 日 2 回の経口投与	day 1～28	day 29～42

体表面積		基準量
1.25 m^2 未満	→	80 mg/day (20 mg x 4 cap)
1.25 m^2 以上 1.50 m^2 未満	→	100 mg/day (25 mg x 4 cap)
1.50 m^2 以上	→	120 mg/day (20 mg x 6 cap)

0.5. 予定登録数と研究期間

予定登録患者数:350 人
登録期間:4 年、追跡期間:登録終了後 5 年、総研究期間:9 年
主たる解析は登録終了後 3 年の時点で行う。
6 か月以内の登録期間の延長は、プロトコール改訂手続き不要とする。

0.6. 問い合わせ先

適格規準、治療変更規準など、臨床的判断を要するもの:研究事務局(表紙、16.6.)
登録手順、記録用紙(CRF)記入など:JCOG データセンター(16.11.)
有害事象報告:JCOG 効果・安全性評価委員会事務局(16.9.)

研究成果の刊行物・別刷

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	小西　大
	古瀬　純司

EXPERT OPINION

Emerging drugs for biliary cancer

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Introduction: The number of biliary cancer patients is small and it is often complicated by serious adverse events making it difficult for clinical studies to be performed on this cancer. However, researches for clarification of the mechanisms of onset and proliferation of biliary cancer and of the effects of drugs suppressing these mechanisms have been initiated recently, with the goal of establishing effective treatments.

Areas covered: This review will cover epidemiological and biological features of biliary cancer, the efficacy and limitations of the existing methods of treatment, and current goals for the development of new treatment methods. Furthermore, the findings of pre-clinical studies on promising treatment targets and ongoing clinical studies are also reviewed, and perspectives for the future of treatment are discussed.

Expert opinion: Following the recent increase in the interest in drug development, attempts at clarifying the molecular mechanisms underlying the onset and proliferation have been made proactively, accompanied by clinical studies on various molecular-targeted drugs for the treatment of this cancer. To demonstrate the efficacy of these drugs, it is essential to establish a system for efficient screening of patients carrying the molecular targets and to devise an excellent clinical study design.

Keywords: biliary cancer, chemotherapy, cholangiocarcinoma, molecular-targeted drugs

Expert Opin. Emerging Drugs [Early Online]

1. Background

The biliary tract consists of the intra-hepatic bile duct, the extra-hepatic bile duct, the gallbladder and the ampulla of Vater. 'Biliary cancer' is a collective term for cancers arising from these organs. According to the UICC Classification, biliary cancer includes extra-hepatic biliary cancer, gallbladder cancer and cancer of the ampulla of Vater, while intra-hepatic biliary cancer is classified as primary liver cancer [1]. This classification is useful in the debate about the appropriate surgical procedure or extent of surgical resection. In terms of the histopathological characteristics, that is, carcinogenesis in the bile duct epithelium and predominance of adenocarcinoma, and clinical features, that is, likelihood of early lymph node metastasis or distant metastasis, intra-hepatic bile duct is akin to biliary cancer rather than to liver cancer. For this reason, intra-hepatic biliary cancer is often counted as biliary cancer when considering the appropriate drug therapy. In practice, many of the clinical studies on chemotherapy for biliary cancer have included intra-hepatic biliary cancer as one of the target diseases. Histologically, biliary cancer has been classified as adenocarcinoma, adenosquamous cell carcinoma, squamous cell carcinoma, small cell carcinoma, adenoendocrine cell carcinoma, etc. Among all cases of biliary cancer, adenocarcinoma accounts for the overwhelming majority (over 90%), followed by adenosquamous cell carcinoma (about 2%) [2].

The incidence of biliary cancer is particularly high in Chile and Japan, followed by Western Asian countries and India. This cancer occurs at a relatively low incidence in Europe and the USA. There are many countries in which the precise statistics about

informa
healthcare

Table 1. Randomized controlled studies evaluating cytotoxic agents in advanced biliary cancer.

Regimens	Stage of development	Number of patients	Response rate (%)	Median survival (months)	p	Authors
5-FU	ND	30	10	NA	NA	Falkson *et al.* [91]
5-FU + STZ		26	13	NA		
5-FU + MeCCNU		31	10	NA		
5-FU	ND	18	0	NA	n.s.	Takada *et al.* [92]
5-FU + ADR + MMC		18	0	NA		
BSC	ND	19	NA	2.5	0.1	Glimelius *et al.* [93]
5-FU + FA + etoposide		18	NA	6.5		
GEM + MMC	rII	25	20	6.7	NA	Kornek *et al.* [94]
Capecitabine + MMC		26	31	9.3		
5-FU	rII	29	7	5	NA	Ducreux *et al.* [95]
5-FU + FA + CDDP		29	19	8		
5-FU + FA + etoposide	III	27	15	12	0.2	Rao *et al.* [96]
5-FU + EPI + CDDP		27	19	9		
GEM	rII	44	15	-	NA	Valle *et al.* [8]
GEM + CDDP		42	24	-		
BSC	ND	27	0	4.5	0.039	Sharma *et al.* [11]
5-FU + FA		28	14	4.6		
GEM + OX		26	31	9.5		
GEM	III	206	16	8.3	< 0.001	Valle *et al.* [9]
GEM + CDDP		204	26	11.7		
GEM	rII	42	12	7.7	NA	Okusaka *et al.* [10]
GEM + CDDP		41	20	11.2		
S-1	rII	50	17	9	0.52	Morizane *et al.* [97]
GEM + S-1		51	36	12.5		
GEM	rII	32	9	9.2	NA	Sasaki *et al.* [98]
GEM + S-1		30	20	8.9		

BSC: Best supportive care; FA: Folic acid; MeCCNU: Methyl-CCNU; NA: Not available; ND: Not described; n.s.: Not significant; rII: Randomized Phase II study; STZ: Streptozosin; III: Phase III study.

patients with biliary cancer are unavailable. The age-adjusted incidence of biliary cancer, excluding intra-hepatic biliary cancer, (per 100,000 population) varies greatly among countries: 10.4 in Chile, 4.9 in Japan and 1.7 in the USA [3]. The incidence of intra-hepatic biliary cancer is markedly high in the Khon Kaen District of Thailand (age-adjusted incidence per 100000 population: 71.3 for males and 34.6 for females). The reported causes of biliary cancer include parasites (at Khon Kaen District), exposure to Thorotrast (thorium dioxide), large gallstones and inflammatory bowel disease [4]. Biliary diseases such as primary sclerosing cholangitis (PSC), cirrhosis, hepato/chole/choledocholithiasis, chronic cholecystitis, chronic non-alcoholic liver disease, and hepatic C virus (HCV) infection are all known to be pre-disposing factors for neoplastic transformation. In most cases of biliary cancer, however, the exact cause is unknown and the large regional variances have not been explained sufficiently.

For biliary cancer, surgical resection is the only modality for radical treatment; however, the percentage of patients undergoing radical resection is not sufficiently high: 68.3% for intra-hepatic biliary cancer, 47.3% for gallbladder cancer, 46.7% for extra-hepatic biliary cancer and 86.6% for cancer of the ampulla of Vater, according to the registries in Japan [5,6]. The prognosis of patients undergoing surgical resection is poor, with reported 5-year survival rates after surgery of 32.7% for intra-hepatic biliary cancer, 41.6% for gallbladder cancer, 33.1% for extra-hepatic biliary cancer and 52.8% for cancer of the ampulla of Vater; these results suggest that complete cure is difficult in patients with this cancer [5,6]. For inoperable cases receiving chemotherapy, the median survival period has recently been reported to be about 8 – 12 months. Thus, the prognosis of patients with biliary cancer is still quite poor at present.

2. Medical need

It is not uncommon for a biliary cancer to be already at an advanced stage at the time of diagnosis. Even in resectable cases, biliary cancer often recurs soon after the surgery. Thus, patients with biliary cancer still have a poor prognosis at present, and development of effective non-surgical therapies is strongly needed. Clinical studies on non-surgical therapies conducted to date are confined to those involving only one group or small-scale comparisons, and there are scarcely any reports of large-scale Phase III trials (**Table 1**). Thus, no non-surgical therapies with satisfactory outcomes had been established until recently. Some of the possible reasons for this status include: i) there are very few known anticancer agents that may be expected to yield high response rates among patients with this cancer; ii) chemotherapy is not

always easy for patients with this cancer, as their general condition is often unstable, which increases their susceptibility to infection or sepsis; iii) large-scale clinical studies are difficult to perform because the number of patients with this cancer is limited; iv) global interest in the development of new treatment methods for this cancer has been limited. Recently, some large-scale Phase III studies were carried out for the first time, demonstrating the effect of some chemotherapies in prolonging the survival period of these patients, and development of molecular-targeted drugs has been successful in patients with non-biliary solid cancers, for which few valid drugs were available until recently. Thus, the interest in the development of new drugs for biliary cancer has recently begun to rise sharply.

3. Existing treatments

Of the chemotherapeutic regimens, single-drug chemotherapy using a drug of the fluoropyrimidine family or gemcitabine has yielded relatively favorable outcomes. As a result, these drugs are now often used as key drugs for the treatment of biliary cancer. Among others, gemcitabine has been authorized in several countries as a drug for insurance-covered treatment of biliary cancer on the basis of the results of Phase II trial [7], and has been extensively used in clinical practice in these countries.

Recently, a Phase III trial comparing gemcitabine monotherapy with combined gemcitabine + cisplatin (GC) therapy was carried out in the United Kingdom, which yielded a more favorable outcome of GC therapy [8,9]. A randomized Phase II trial using the same regimen carried out in Japan also yielded a similar outcome [10]. On the basis of these results, GC therapy is now positioned as a standard therapy for advanced biliary cancer. Combined gemcitabine + oxaliplatin (GEMOX) therapy was adopted as the control therapy in some Phase III trials, on the ground that oxaliplatin is classified as an anticancer drug of the platinum family to which cisplatin also belongs, and that a randomized comparative trial revealed a longer survival period following this therapy than following symptomatic therapy or combined 5-FU + folinic acid therapy [11]. However, the randomized study evaluating the survival-prolonging effects of GEMOX therapy was a small-scale study involving only patients with gallbladder cancer (n = 88), and there is no published randomized study comparing this therapy with gemcitabine monotherapy, that is a community standard in the past, or GC therapy, that is the current standard therapy. Even at present, with the availability of an established standard therapy, the median survival period of patients with advanced biliary cancer is quite short, < 1 year. Thus, development of a more effective treatment method is keenly desired.

As far as second- and subsequent-line treatments are concerned, no randomized comparative studies have been made, and no treatment method has been established yet as standard second- or subsequent-line therapy. Also no standard adjuvant therapies with established usefulness from randomized studies have been reported yet for surgically treated cases.

4. Current research goals

As stated above, standard therapy for biliary cancer was established for the first time only recently, although the history of drug development for biliary cancer is quite short as compared to that for other types of cancer. Other than the key drugs, that is, gemcitabine, drugs of the platinum family and drugs of the fluoropyrimidine family, there is no drug that has been fully recognized to be effective against biliary cancer. Moreover, the effects of these key drugs against biliary cancer are also limited. Thus, the most important goal at present is to develop new drugs that would improve prognosis in patients with this cancer.

The study comparing GEMOX + erlotinib combination therapy with GEMOX therapy in patients with advanced biliary cancer is the only Phase III trial reported after GC therapy was prolong the survival period and was positioned as a standard therapy [12]. That study adopted survival period as the primary endpoint and was designed to examine whether or not the addition of erlotinib to GEMOX would contribute to survival prolongation. Unfortunately, the median survival period was 7.5 months in both groups, without any significant inter-group difference. Phase III trials now under way include: i) a study in Korea designed to compare GEMOX therapy with capecitabine + oxaliplatin (XELOX) therapy (NCT01470443) and ii) a study in Japan designed to compare GC therapy with gemcitabine + S-1 therapy (UMIN000010667). The primary endpoint is progression-free survival in the former study, and overall survival in the latter. Phase III studies of post-operative adjuvant therapy now under way are: i) a study in the United Kingdom designed to compare the outcome of surgery alone with that of patients receiving capecitabine as post-operative adjuvant therapy, with the 2-year survival rate adopted as the primary endpoint (NCT00363584), ii) a study in Japan designed to compare the outcome of surgery alone with that of patients receiving S-1 as post-operative adjuvant therapy, with overall survival adopted as the primary endpoint (UMIN000011688), iii) a study in France designed to compare the outcome of surgery alone with that of patients receiving GEMOX therapy as post-operative adjuvant therapy, with recurrence-free survival adopted as the primary endpoint (NCT01313377), and iv) a study in Japan designed to compare the outcome of surgery alone with that of patients receiving gemcitabine as post-operative adjuvant therapy involving only patients with extra-hepatic biliary cancer, with overall survival adopted as the primary endpoint (UMIN000000820).

5. Scientific rationale

Biliary carcinogenesis is considered to follow the sequence of dysplasia followed by hyperplasia of the bile duct epithelium; however, these processes have not yet been fully clarified. To

Table 2. Overexpression frequencies of growth factors and their receptors in biliary cancer.

Target	Positive rate %	
	Extra-hepatic biliary cancer*	Intra-hepatic biliary cancer
EGFR [15-18]	0 – 19.2	10.7 – 81.3
HER2 [15-20]	5.1 – 15.7	0 – 81.3
VEGF [15,39,40,50]	31.4 – 59.2	53.8 – 100
c-Met [16,19,49-51]	0 – 80.8	21.4 – 57.7
HGF [50]	0 – 7.7	-

Reproduced from Ojima [21].
*Extra-hepatic biliary cancer, including gallbladder cancer and carcinoma of ampulla of Vater.

date, the involvement of several molecular pathways in the onset and proliferation of biliary cancer has been suggested. These pathways are expected to serve as potential targets for the treatment of biliary cancer (Table 2).

Epidermal growth factor receptor (EGFR) and human EGFR-2 (HER2) are members of the ErbB receptor tyrosine kinase family. The binding of ligands, such as epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α), to their extracellular ligand-binding domains initiates intracellular signaling cascades, leading to the progression, proliferation, migration and survival of cancer cells [13,14]. The proportion of previously reported EGFR-positive and HER2-positive cases has varied from 0 – 81.3% [15-18] and 0 – 81.8% [15-20], respectively, in biliary cancer. These values vary depending on the number of cases, the locations of the tumors and the antibodies that were used [21]. Yoshikawa *et al.* reported that EGFR overexpression was a significant prognostic factor and also a risk factor for tumor recurrence in intra-hepatic biliary cancer [15]. Ito *et al.* reported that EGFR expression was related to lymph node metastasis, aberrant p53 expression, proliferative activity and carcinoma differentiation [18]. Therefore, EGFR contributes greatly to biliary cancer progression. In contrast to EGFR, studies have reported that HER2 is significantly expressed in well-differentiated, non-invasive cancers [15], and is found in proliferative biliary epithelium and atypical epithelium in patients with hepatolithiasis, a risk factor for biliary cancer [19]. These findings suggest that HER2 and EGFR expression in biliary cancer is distinctively associated with biliary cancer. Yoshikawa *et al.* also showed that the TKKK cell line, which exhibits EGFR gene amplification, was sensitive to vandetanib, a multi-tyrosine kinase inhibitor that targets EGFR and vascular endothelial growth factor receptor-2 (VEGFR-2), whereas the OZ and HuCCTI cell lines, which harbor KRAS mutations, were resistant. These results suggest that EGFR gene amplification could be a predictive biomarker for anti-EGFR therapy, and even if EGFR phosphorylation is inhibited, KRAS mutations result in the constitutive activation of the downstream RAS/RAF/Grb2-Ras-mitogen-activated protein kinase (MAPK) signaling pathway, leading to treatment resistance (Table 3).

The RAS/RAF/extracellular-regulated kinase (ERK) signaling pathway plays a central role in the regulation of many cellular processes, including proliferation, survival, differentiation, apoptosis, motility and metabolism [22-24]. This pathway is activated by a diverse group of extracellular signals, including growth factor receptors like EGFR. Mutation and constitutive activation of the oncogene KRAS have also been reported in about 10 – 50% of biliary cancers [25-33]. Relatively higher percentages of KRAS mutation have been reported in East Asian countries, and lower percentages have been seen in Western countries, a result that might be explained by geographical differences in etiology or ethnicity. B-RAF mutation has been recognized in 8.1 – 33% of patients with biliary cancer [25,33-35]. Activated RAS triggers the phosphorylation and activation of RAF kinase, which then phosphorylates mitogen-activated ERK1 (MEK1) and MEK2 on two serine residues [27,36]. Activated MEK phosphorylates its only known substrates, ERK1 and ERK2. Phosphorylated ERK (pERK) dimerizes and translocates to the nucleus [37], where it is involved in several important cellular functions [27]. A pre-clinical study in a murine orthotopic model using a human gallbladder cell line harboring a KRAS mutation exhibited constitutive MAPK activation and the progression of gallbladder cancer; a MEK inhibitor (U0126), significantly prolonged the survival of the mice, compared with untreated controls [38].

VEGF plays a key role in tumor-associated neo-angiogenesis, which contributes to providing tumors with oxygen, nutrition and a route for metastasis. The proportion of previously reported VEGF-positive cases has varied from 31.4 to 100% for biliary cancer [15,39-41]. A high microvessel density (MVD) is reportedly a prognostic factor in biliary cancer [42,43] and is associated with VEGF expression in intra-hepatic biliary cancer [39]. Indeed, VEGF expression is significantly associated with intra-hepatic metastasis in intra-hepatic biliary cancer [15]. These facts suggest that VEGF plays an important role in the process of biliary cancer metastasis by promoting angiogenesis.

Hepatocyte growth factor (HGF) is a cytokine that acts as a growth factor in biliary cancer, and cancer cells themselves produce HGF to activate their proliferation [44,45]. The effects of HGF are transmitted through its receptor, c-Met, and the activation of HGF/c-Met signaling initiates cell invasiveness and triggers metastasis through the direct involvement of tumor angiogenesis [46]. Upon ligand binding, c-Met activates multiple downstream signal transduction pathways, including the MAPK cascade, the phosphatidylinositol-3 kinase (PI3K) pathway, and the signal transducer and activator of transcription (STAT) pathway [47,48]. The proportion of previously reported c-Met-positive cases has varied from 0 to 80.8% (Table 3) [16,19,49-51]. Immunohistochemical c-Met overexpression has been reported in hyperplastic as well as dysplastic epithelial cells of human hepatic bile ducts [19,51].

Table 3. Clinical trials evaluating molecular-targeted agents in advanced biliary cancer.

Compound	Targets	Regimen	Stage of development	Indication	No.	RR (%)	MST (months)	p	Authors
Erlotinib	EGFR	Erlotinib	II	1st/2nd	42	8	7.5	-	Philip *et al.* [73]
		GEM + OX	III	1st	133	16	9.5	0.61	Lee *et al.* [12]
		GEM + OX + erlotinib			135	30	9.5		
Cetuximab	EGFR	Cetuximab	Case series	Any	5	80	NA	-	Chang *et al.* [74]
		GEM + OX + cetuximab	II	1st	30	63	15.2	-	Gruenberger *et al.* [26]
		GEM + OX	rII	1st	74	29	12.4	0.19	Malka *et al.* [75]
		GEM + OX + cetuximab			76	23	11		
Panitumumab	EGFR	GEM + OX + CAP + panitumumab	II	1st	46	33	10	-	Jensen *et al.* [76]
Lapatinib	EGFR1, ErbB2	Lapatinib	II	1st/2nd	17	0	5.2	-	Ramanathan *et al.* [77]
		Lapatinib	II	1st/2nd	9	0	5.1	-	Peck *et al.* [78]
Bevacizumab	VEGF	GEM + OX + bevacizumab	II	1st	35	40	12.7	-	Zhu *et al.* [79]
		Erlotinib + bevacizumab	II	1st	49	18	9.9	-	Lubner *et al.* [80]
Sorafenib	VEGFR, PDGFR, c-KIT, Flt-3, RET	Sorafenib	II	Any	46	2	4.4	-	Bengala *et al.* [81]
		Sorafenib	II	1st	36	0	9	-	El-Khoueiry *et al.* [82]
		Sorafenib + erlotinib	II	1st	32	7	6	-	El-Khoueiry *et al.* [83]
		CAP + OX + sorafenib	I	1st/2nd	16	13	-	-	LoConte *et al.* [99]
Sunitinib	VEGFR, PDGFR, KIT, Flt-3, RET	Sunitinib	II	Any	56	9	13	-	Yi *et al.* [86]
Selumetinib	MEK1/2	Selumetinib	II	1st/2nd	28	12	9.8	-	Bekaii-Saab *et al.* [27]
ARRY-438162	MEK1/2	ARRY-438162	I	2nd/later	28	7	-	-	Finn *et al.* [100]
Bortezomib	NF-κB	Bortezomib	II	Any	20	5	9.3	-	Costello *et al.* [87]
Imatinib	Bcr-Abl, v-abl, c-abl, PDGFR	Imatinib	II	2nd	9	0	4.9	-	Roth *et al.* [88]

1st: First line; 2nd: Second line; CAP: Capecitabine; CDDP: Cisplatin; GEM: Gemcitabine; MST: Median survival time; NA: Not available; No.: Number of patients; OX: Oxaliplatin; RR: Response rate.

Furthermore, positive immunostaining for c-Met is highest among well-differentiated intraductal tumors and is relatively low in poorly differentiated invasive tumors [51]. Miyamoto *et al.* reported that a high c-Met expression level was significantly correlated with EGFR expression and the overall 5-year survival rate for patients with biliary cancer who had undergone curative surgery [49].

Transforming growth factor-beta (TGF-β) acts as a potent growth inhibitor for normal biliary epithelial cells. However, in many malignant tumors including biliary cancer, abnormalities reportedly occur at some steps of the TGF-β signal transduction pathway, resulting in cancer cell proliferation and progression [52,53]. Zen *et al.* showed that TGF-β1 was expressed as a diffuse and granular cytoplasmic staining pattern in hyperplastic biliary epithelium (70%), dysplastic epithelium (100%), intraductal papillary neoplasm of the bile duct (100%) and intra-hepatic biliary cancer with dysplasia (89%) or intraductal papillary neoplasm of the bile duct (86%), and the majority of these epithelial cells were positive, when detected. However, its expression was not observed in normal bile ducts [54]. Benckert *et al.* showed that both TGF-β1 and VEGF were overexpressed, suggesting that TGF-β1 can stimulate VEGF gene transcription in malignant cholangiocytes in a paracrine and/or autocrine manner through a Sp1-dependent mechanism [40]. In addition, the inhibition of interleukin-6 (IL-6) signaling [55] and cyclin D1 expression [54] using siRNA resulted in the disappearance of the biliary cancer growth-promoting effect of TGF-β, suggesting that IL-6 and cyclin D1 are closely involved in the promotion of cancer cell growth by TGF-β.

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes that, when altered, promote carcinogenesis. IDH1 and IDH2 are $NADP^+$-dependent enzymes that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) [56-64]. Somatic mutations in IDH1/2 result in proteins with neomorphic enzyme activity that allows α-KG to be more effectively converted to 2-hydroxyglutarate (2-HG). Increased levels of 2-HG are thought to promote carcinogenesis by competitively inhibiting enzymes that use α-KG as a cofactor [56,65-68]. Borger *et al.* reported that mutations in IDH1 and IDH2 were found only in intra-hepatic biliary cancer (9 of 40, 23%) and in none of extra-hepatic biliary and gallbladder cancers [69]. Kipp *et al.* showed that the mutations were identified in 21 (22%) of 94 biliary cancer specimens; they were more frequently observed in intra-hepatic biliary cancer compared with extra-hepatic cancer (28 vs 7%, respectively; $p = 0.03$) [56]. These findings may provide new insights into pathogenesis and therapeutic targeting for this disease.

Recently, Wu *et al.* and Arai *et al.* reported that some patients with biliary cancer harboring gene rearrangements of FGFR2 have been identified [70,71]. Cells harboring FGFR fusions showed enhanced sensitivity to FGFR inhibitors, suggesting that patients with cancer with FGFR fusions may benefit from targeted FGFR kinase inhibition. Gu *et al.* confirmed the presence of ROS kinase fusions in 8.7% (2 out of 23) of intra-hepatic biliary cancer patients [72]. The expression of ROS fusions in 3T3 cells confers a transforming ability both *in vitro* and *in vivo* and is responsive to its kinase inhibitor. These studies have suggested that FGFR and ROS kinases are new promising candidates for therapeutic targets in biliary cancer and suggest that other 'actionable' therapeutic targets may be identified in patients with biliary cancer in the near future.

6. Competitive environment

Studies have been conducted to clarify the mechanism underlying the onset and proliferation of biliary cancer, accompanied by efforts directed at the development of molecular-targeted drugs for the treatment of this cancer. To date, however, no molecular-targeted drug that can be positioned as standard therapy has been developed yet (Table 3). In many regions, the number of patients with biliary cancer is small and there has not been sufficient interest in conducting clinical studies aimed at developing new drugs for this cancer. Recently, however, a standard therapy has been established on the basis of the results of large-scale studies, which has stimulated the development of better treatment methods for biliary cancer. Furthermore, the systems for clinical trials have recently been improved in Asian and South American countries in which biliary cancer occurs at a elatively high incidence. Under such circumstances, many programs for the development of new drugs of the molecular-targeted drug category have been started (Table 4).

6.1 Drugs primarily targeting EGFR or HER2

6.1.1 Erlotinib

Biliary cancer has long been reported to show high expression levels of EGFR and its ligand, suggesting that EGFR inhibitors may exert efficacy against biliary cancer. Erlotinib, an EGFR tyrosine kinase inhibitor, is the first drug that has been shown, when administered in combination with gemcitabine, to prolong the survival period of patients with inoperative pancreatic cancer significantly than gemcitabine monotherapy. A clinical study of this molecular-targeted drug in patients with biliary cancer has been started earlier than such a study of any other drug of this category.

In regard to erlotinib monotherapy, a Phase II trial was carried out in 42 patients with inoperative biliary cancer (including 57% with a history of prior treatment), which yielded 3 responders (8%) and a median survival period of 7.5 months, suggesting the necessity of using this drug in combination with some other drug [73].

In Korea, a Phase III trial was carried out for evaluating the effects of addition of erlotinib to GEMOX therapy through comparison of the GEMOX + erlotinib group (n = 135) and the GEMOX group (n = 133). The results of this study were reported in 2012, and the response rate was significantly higher in the GEMOX + erlotinib group (30 vs 16%,

Table 4. Molecular-targeted agents undergoing clinical trials in advanced biliary cancer.

Compound	Company	Primary targets	Other targets	Regimens	Stage of development	Indication	Trial
Erlotinib	OSI Pharmaceuticals	EGFR		GEM + OX + erlotinib	Ib	1st line	NCT00987766
Cetuximab	ImClone	EGFR		GEM + OX	rII	1st line	NCT01267344
				GEM + OX + cetuximab			
Panitumumab	Amgen	EGFR		GEM + OX + panitumumab	II	1st line	NCT01308840
				GEM + OX	rII	1st line	NCT01389414
				GEM + OX + panitumumab			
				GEM + CPT-11 + panitumumab	II	1st line	NCT00948935
				GEM + CDDP	rII	1st line	NCT01320254
				GEM + CDDP + panitumumab			
Afatinib	Boehringer Ingelheim	EGFR	HER2	GEM + CDDP + afatinib	I	1st line	NCT01679405
Bevacizumab	Roche	VEGF		mFOLFOX6 + bevacizumab	II	1st line	NCT00881504
				GEM + CAP + bevacizumab	II	1st line	NCT01007552
Sorafenib	Bayer	VEGFR	PDGFR, c-KIT,	GEM + OX + sorafenib	I-II	1st line	NCT00955721
			Flt-3, RET	GEM + CDDP + sorafenib	II	1st line	NCT00919061
				GEM	rII	1st line	NCT00661830
				GEM + sorafenib			
Cediranib	AstraZeneca	VEGFR		GEM + CDDP	rII	1st line	NCT00939848
				GEM + CDDP + cediranib			
				mFOLFOX6 + cediranib	II	1st line	NCT01229111
Vandetanib	AstraZeneca	VEGFR-2	EGFR	Vandetanib	rII	1st line	NCT00753675
				GEM			
				GEM + vandetanib			
				GEM + CAP + vandetanib	I	unknown	NCT00551096
Selumetinib	AstraZeneca	MEK1/2		GEM + CDDP + selumetinib	I/II	1st line	NCT01242605
GSK1120212	GlaxoSmithKline	MEK1/2		GEM + GSK1120212	I	unknown	NCT01324258
MEK162	Novartis	MEK1/2		GEM + CDDP + MEK162	I/II	1st line	NCT01828034
Everolimus	Novartis	mTOR		Everolimus	II	1st line	NCT00973713
MK2206	Merck	Akt		MK2206	II	2nd line	NCT01425879

CAP: Capecitabine; CDDP: Cisplatin; GEM: Gemcitabine; ND: Not described; OX: Oxaliplatin.

p = 0.005). The progression-free survival (primary endpoint) tended to be better in the combined therapy group (median: 5.8 vs 4.2 months, HR = 0.80, p = 0.087), although there was no marked difference in the overall survival (median: 9.5 months vs 9.5 months, HR = 0.93, p = 0.61) [12].

6.1.2 Cetuximab

Cetuximab is a monoclonal antibody to EGFR. It competes with EGF in binding with EGFR, thereby blocking the transduction of EGFR signaling. With these features, cetuximab may be expected to exert comparable efficacy to erlotinib against biliary cancer.

Concerning cetuximab monotherapy for biliary cancer, a case report covering five cases has been published, which indicated a rather promising outcome of this treatment: complete response in one case and partial response in three cases [74]. A Phase II trial on GEMOX + cetuximab therapy was also carried out, which reported a response rate of 63% (19/30 cases), including complete response in three cases (10%) and reduction of the tumor size to an extent allowing surgical resection in nine cases (30%), thereby suggesting the need of further evaluation of this therapy on the basis of these promising results [26]. Subsequent to this study, a randomized Phase II trial was carried out comparing GEMOX + cetuximab group (n = 76) and the GEMOX group (n = 74). The results of this study were reported at the meeting of American Society of Clinical Oncology (ASCO) in 2012, and the 4-months progression-free survival rate (primary endpoint) exceeded the target (60%) in the GEMOX + cetuximab group; however, contrary to expectation, there was no evident difference between the two groups in the response rate (GEMOX + cetuximab group vs GEMOX group: 23 vs 29%), progression-free survival (median: 6.0 months vs 5.3 months) or overall survival (median: 11.0 vs 12.4 months) [75]. A similar randomized Phase II trial is also now under way in Taiwan.

6.1.3 Panitumumab

Panitumumab is also a monoclonal antibody to EGFR. However, unlike cetuximab, which is a human : mouse chimeric antibody, panitumumab is a human monoclonal antibody associated with a lower incidence of adverse reactions arising from allergic mechanisms. A Phase II trial of regimens, including GEMOX + panitumumab and GC + panitumumab is now under way [76].

6.1.4 Lapatinib

Lapatinib serves as a tyrosine kinase inhibitor for EGFR and HER2/neu (ErbB-2, EGFR type 2), and biliary cancer is known to express EGFR and HER2; therefore, the drug is expected to exert efficacy against biliary cancer. A Phase II trial was carried out in patients with hepatobiliary cancer (including 19 patients with biliary cancer and 30 patients with liver cancer), which yielded no responders and a poor overall survival (median: 5.2 months) [77]. Also, in a Phase II trial involving only patients with biliary cancer, the response was poor (0%), necessitating premature discontinuation of the trial [78].

6.2 Drugs primarily targeting VEGFR

6.2.1 Bevacizumab

VEGF and its receptor (VEGFR) are highly expressed in many types of cancer and serve as important targets for molecular-targeted therapy. The efficacy of these signal transduction inhibitors is expected also in patients with biliary cancer. Bevacizumab is a monoclonal antibody to VEGF and inhibits VEGF activity through binding to VEGF.

A Phase II trial of GEMOX + bevacizumab therapy has been carried out, which yielded a favorable outcome, that is, of response in 14 (40%) of the 35 patients and a median overall survival of 12.7 months [79]. A Phase II trial of erlotinib + bevacizumab therapy has also been carried out, which yielded a response in only 6 (12%) of the 49 patients and a median overall survival of 9.9 months [80]. This result suggests add-on effects of bevacizumab as compared to erlotinib monotherapy evaluated in a previous Phase II trial.

Thus, the effects of bevacizumab on biliary cancer have been evaluated only in single-arm studies, with no randomized study performed to date.

6.2.2 Sorafenib

Sorafenib has been shown to inhibit the tyrosine kinase activity of VEGFR and platelet-derived growth factor receptor (PDGFR) involved in angiogenesis, to inhibit the serine/threonine kinase activity of C-Raf and B-Raf, which constitute the Raf/MEK/ERP pathway, a pathway for signal transduction related to cell proliferation, and to inhibit many other signal transduction pathways such as stem-cell growth factor receptor (c-KIT) and Fms-like tyrosine kinase 3 (Flt-3). Reports have been published on the effects of sorafenib in prolonging the survival period of patients with kidney or liver cancer, and multiple clinical studies have been conducted on the basis of the expectation of the effects of this drug against biliary cancer. Two Phase II trials of sorafenib monotherapy have been carried out, with the response rate being low (0 – 2%) in both trials and the median overall survival differing between the two trials (4.4 vs 9.0 months) [81,82].

A Phase II trial of erlotinib + sorafenib therapy has also been carried out. Response was seen in 2 (7%) of the 32 patients, but both the progression-free survival (median: 2 months) and the overall survival (median: 6 months) were poor, failing to endorse reinforcement of the efficacy of a combination of these two drugs [83]. A randomized Phase II trial is now under way for evaluation of combined sorafenib + gemcitabine therapy, in comparison with placebo + gemcitabine therapy [84].

6.2.3 Cediranib

Cediranib is a new tyrosine kinase inhibitor of VEGFR. A randomized Phase II trial comparing GC + cediranib therapy with GC therapy is now under way primarily in the United

Kingdom [85]. A Phase II trial on 5-fluorouracil (5-FU) + leucovorin + oxaliplatin (modified FOLFOX6) + cediranib therapy is now under way in the USA.

6.2.4 *Vandetanib*

Vandetanib inhibits VEGFR2 tyrosine kinase and EGFR tyrosine kinase. A randomized Phase II trial comparing vandetanib + gemcitabine or placebo + gemcitabine or vandetanib monotherapy was carried out in Italy, although its results have not yet been reported.

6.2.5 *Sunitinib*

Sunitinib is a molecular-targeted drug capable of inhibiting the tyrosine kinase of numerous receptors such as VEGFR, PDGFR, c-Kit, rearranged during transfection (RET), colony-stimulating factor 3 (CSF-3) and Flt-3. Its effectiveness against kidney cancer and KIT (CD117)-positive gastrointestinal stromal tumor has been demonstrated. When this drug was used as second-line treatment for patients showing resistance to primary gemcitabine-based or 5-FU-based treatment, the response rate was 8.9%. Median progression-free survival was 1.9 months and median overall survival was 4.8 months [86].

6.3 Drugs primarily targeting MEK

6.3.1 *Selumetinib*

Selumetinib is an MEK 1/2 inhibitor, that is, a mitogen-activated ERK 1/2 inhibitor. A Phase II trial of selumetinib monotherapy has been carried out. The study involved 28 patients with inoperable biliary cancer, including 39% with a history of prior treatment. Response was seen in three cases (12%), including one case of complete response and two cases of partial response. The median progression-free survival was 3.7 months and the medial overall survival was 9.8 months. Thus, relatively favorable outcome of this monotherapy was obtained as compared to that of other drug monotherapies [27].

6.4 Other targets

Basic studies have revealed activation of mammalian target of rapamycin (mTOR), BRAF, c-MET (HGF receptor), nuclear factor-kappa B (NF-κB), KIT, etc., in patients with biliary cancer. Following these reports, clinical studies have been carried out of everolimus (mTOR inhibitor), bortezomib (NF-κB inhibitor) [87], imatinib (c-KIT inhibitor) [88], etc.

7. Potential development issues

In many regions biliary cancer is a rare disease, and even in regions where there are numerous patients because there are many countries in which an adequate healthcare system or cancer registry system has not been developed, the actual state of affairs, including the epidemiology of biliary cancer, its clinical characteristics, patients' outcome, etc., has never been fully clarified. Physicians' and patients' awareness of biliary cancer is not always high, and it is not uncommon for it to be misdiagnosed as liver cancer, pancreatic cancer or cancer whose primary site is unknown. Because the history of drug development for biliary cancer has been short and there has been little information or experience in regard to basic or clinical researches, a number of issues in regard to drug development remain unresolved, and the issues that seem to be considered particularly important are as follows.

7.1 Patient selection

Almost all of the current clinical trials regarding biliary cancer are being conducted on unselected patient populations. However, despite being the same biliary cancer, there is diversity at the molecular level, and there may be large differences in drug sensitivity [89,90]. Consequently, it is important to discover gene mutations or biomarkers that will make it possible to predict drug sensitivity and side effects, and to conduct clinical trials by selecting patients according to differences in their expression. The fact that biliary cancer develops deep in the body and adjacent to important organs makes it difficult to collect tissue, but as a result of repeated efforts to do so, the diversity of biliary cancer will become clearer, and the likelihood of success in developing drugs for the treatment of biliary cancer should increase.

7.2 Development of a clinical trial system and fostering personnel

High-quality clinical trials are indispensable to accurately evaluating the efficacy and safety of drugs, and it is important to develop a clinical trial system. Biliary cancer is a common disease in South America and Asia, and in many of the countries the clinical trial system is inadequate and there are extremely few medical oncologists who are familiar with biliary cancer. Nevertheless, there are also many regions in these countries that are developing economically, and in the future progress is expected in developing healthcare and a clinical trial system and in fostering personnel. Moreover, because concern about drug development for biliary cancer is also increasing in Western countries, where there is little biliary cancer, case accumulation for clinical trials is expected to be pursued efficiently.

7.3 Management of complications

Many biliary cancer patients have serious complications, that is, jaundice, liver dysfunction, cholangitis, liver abscesses and sepsis. Properly controlling these complications is important to the effective and safe conduct of drug therapy. Consequently, in order for drug development for biliary cancer to flourish, it is important to construct a team healthcare system consisting of a medical oncologist and an interventional radiologist, endoscopist, etc., who have a high level of technical expertise that is capable of controlling these complications.

Only biliary cancer cases with no or mild jaundice or liver dysfunction are currently considered eligible for inclusion in clinical trials. However, there are quite a few cases of biliary cancer in which the jaundice or liver dysfunction cannot be sufficiently improved even by performing biliary drainage, and there is a great need from a clinical standpoint to develop treatments for patients with these complications. In the future, it will be important to pursue the development of drugs for cases with jaundice and liver dysfunction as complications according to the level of specificity and efficacy of drugs pharmacologically, and such attempts are expected to also expand to the establishment of drug therapy for the purpose of improving jaundice and liver function (management of complications with drugs).

8. Conclusion

On the basis of the results of Phase III clinical trials in patients with inoperable biliary cancer, GC therapy has recently been positioned as a standard global therapy for this cancer. However, patients with biliary cancer still have a rather poor prognosis at present, and the sensitivity of this cancer to existing drug therapies is very low. For these reasons, much has been expected of the development of drugs with new mechanisms of actions, such as molecular-targeted drugs, and at present, clinical trials are under way to determine the efficacy of these agents like EGFR inhibitors, VEGFR inhibitors, MEK inhibitors, etc. Genetic aberrations that are likely to provide a clue to the development of new treatment methods, such as ROS fusion gene and FGFR fusion gene, have also been recently detected in patients with biliary cancer. Although the findings collected to date on the development of new drugs for biliary cancer are still limited, both from pre-clinical and clinical studies, information on the mechanisms of onset and proliferation of biliary cancer has been gradually accumulated, which may contribute from now on to the development of new drugs suppressing these mechanisms and establishment of more effective treatment methods if applied to more appropriately selected patients.

9. Expert opinion

Patients with biliary cancer still have a very poor prognosis at present, and this cancer is likely to aggravate rapidly and to be complicated by obstructive jaundice, hepatic dysfunction, cholangitis, sepsis, etc. Thus, this is an intractable type of cancer. Recently, GC therapy has been positioned as a standard therapy for inoperable biliary cancer. However, there are many patients who are still unable to receive even this standard therapy because of the difficulty in controlling the complications, and it is difficult to apply drug therapy for biliary cancer safely and effectively without team care with close cooperation among members having experience in dealing with this cancer, including medical oncologists, gastroenterologists, interventional radiologists, psycho-oncologists, palliative care physicians and nurses. Such a closely cooperative healthcare system is indispensable for the development of new treatment methods for biliary cancer.

Drug therapy so far proved to be effective against biliary cancer pertains only to first-line treatment for inoperable cases, and there is no established standard therapy applicable as second- or subsequent-line therapy or as post-operative adjuvant therapy for resected cases. The current goal of research and development on new drug therapy for biliary cancer is prolongation of the survival of the patients, and in the future, the goal of such efforts will be improvement in the cure rate and the patient's quality of life (QOL). Basic and clinical studies are now being carried out toward the goal of establishing more effective and less toxic methods of primary treatment and establishing a standard method for secondary treatment or adjuvant therapy reliably expected to prolong the survival period. Accumulation of findings as to the mechanism for onset and proliferation of biliary cancer is indispensable for the development of new drugs focusing on molecular-targeted drugs. Also concerning biliary cancer, clinical studies of EGFR, VEGFR and MEK inhibitors and, more recently, other molecular-targeted drugs have been started, with reports available on actionable gene mutations such as FGFR fusion gene and ROS fusion gene. Thus, there is a growing expectation of the establishment of new treatment methods for biliary cancer. However, basic and clinical findings obtained so far are still inadequate as compared with those obtained for other types of cancer, thus indicating the importance of collaboration and activation of research institutions and their linkage to pharmaceutical companies. The number of patients with biliary cancer is particularly large in Asian and South American countries, where economic growth is currently appearing. In these emerging countries, the demand for research and treatment of biliary cancer may be expected to increase, and therefore, for pharmaceutical companies, development of new drugs in this field, in which few effective drugs are available at present, will become an important strategy from now on.

As findings are accumulated concerning biliary cancer, an increase in the discovery of 'driver' mutations and 'actionable' therapeutic targets is expected. However, the percentage of biliary cancer patients having such targets who may respond better to treatment is not generally expected to be high. Because the number of patients with biliary cancer is small in many countries such as Western countries, efficient screening of patients having therapeutic targets and establishment of a system for smooth clinical trials are more important for biliary cancer than for other types of cancer. It is also important to establish the methodology for clinical studies (appropriate endpoint setting, judgment of the necessity of randomization, etc.) when efforts are made to develop drugs expected to be highly effective in a small number of patients.

Declaration of interest

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Twenty-six Cases of Advanced Ampullary Adenocarcinoma Treated with Systemic Chemotherapy

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Objective: Ampullary adenocarcinoma is a rare disease entity and little information regarding these tumors is available. The aim of the present study was to clarify the treatment outcome of systemic chemotherapy in patients with advanced ampullary adenocarcinoma.
Methods: This study consisted of a retrospective review of data obtained from patients diagnosed as having advanced ampullary adenocarcinoma who received non-surgical treatment at a single institution between 1997 and 2010.
Results: We identified 26 patients (15 men, 11 women; median age, 62.0 years) who received treatment for advanced ampullary adenocarcinoma. Twelve patients had Stage IV disease and 14 had recurrences. The chemotherapy regimens consisted of 5-fluorouracil-based regimens (5-fluorouracil + cisplatin, $n = 3$; tegafur-uracil + doxorubicin, $n = 5$ and tegafur, gimeracil and oteracil potassium, $n = 3$) and gemcitabine-based regimens (gemcitabine, $n = 10$ and gemcitabine + cisplatin, $n = 5$). The overall response rate was 7.7%. The median progression-free survival period was 3.2 months (2.5 months in the 5-fluorouracil group vs. 3.5 months in the gemcitabine group), and the median overall survival time was 9.1 months (8.0 months in the 5-fluorouracil group vs. 12.3 months in the gemcitabine group). The median overall survival was significantly longer in stage IV disease than in recurrent disease. The histological phenotype was determined in 10 of the 26 patients. Eight patients had intestinal-type adenocarcinomas and remaining two patients had pancreatobiliary-type adenocarcinomas.
Conclusions: The treatment outcome of patients with advanced ampullary adenocarcinoma was poor. Further development of novel treatments is necessary to improve the prognosis.

Key words: ampullary adenocarcinoma – chemotherapy – 5-fluorouracil – gemcitabine – histological phenotype

INTRODUCTION

Ampullary carcinoma is a particularly uncommon neoplasm. Between 1985 and 2005, the incidence of ampullary carcinoma in the USA was 0.7 cases per 10 000 males and 0.4 cases per 10 000 females (1), accounting for 0.5% of all gastrointestinal malignancies (2). The number of annual deaths because of ampullary carcinoma is only 100–200 in the USA and 800–900 in Japan (http://www.who.int/healthinfo/morttables/en/). This inconsistency in the number of annual deaths may be due to the different geographical regions.

Compared with other periampullary adenocarcinomas, ampullary adenocarcinomas is associated with a higher likelihood of resectability and a more favorable prognosis. Among patients who undergo radical resection, the overall 5-year survival rate ranges from 35 to 46%, which is better than that for patients with distal biliary adenocarcinomas (5-year survival