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 postoperative 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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disclosure

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Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials

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Background: Two recent studies (ABC-02 [UK] and BT22 [Japan]) have demonstrated the superiority of cisplatin and gemcitabine (CisGem) chemotherapy over gemcitabine (Gem) alone for patients with pathologically proven advanced biliary tract cancer (BTC: cholangiocarcinoma, gallbladder and ampullary cancers). This pre-planned analysis evaluates the efficacy of CisGem with increased statistical power.

Patients and methods: We carried out a meta-analysis of individual patient-level data of these studies to establish the effect of CisGem versus Gem on progression-free survival (PFS), overall survival (OS) and carried out exploratory subgroup analyses.

Results: CisGem demonstrates a significant improvement in PFS [hazard ratio (HR) = 0.64, 95% confidence interval (CI) 0.53–0.76, $P < 0.001$] and OS (HR = 0.65, 95% CI 0.54–0.78, $P < 0.001$) over Gem. This effect is most marked among

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patients with good performance status (PS 0–1): HR for PFS is 0.61 (95% CI 0.51–0.74), $P < 0.001$ and OS HR = 0.64 (95% CI 0.53–0.77), $P < 0.001$. CisGem resulted in improved PFS and OS for intra- and extra-hepatic cholangiocarcinomas and gallbladder cancer. The treatment effect between UK and Japanese patients was consistent with respect to OS (HR = 0.65, 95% CI 0.53–0.79 and 0.65, 95% CI 0.42–1.03, respectively); with similar OS in the combination arms (median 11.7 and 11.1 months, respectively). Subgroups least likely to benefit included patients with ampullary tumours and poor performance status (PS2).

Conclusions: CisGem is the standard of care for the first-line treatment of good-PS patients with advanced BTC regardless of ethnicity. Future studies should aim to enhance the effectiveness of this regimen in the first-line setting, establish the role of subsequent (second-line) therapy and assess the role of rationally developed molecular-targeted therapies.

Key words: biliary tract cancer, cholangiocarcinoma, gallbladder cancer, cisplatin, gemcitabine

introduction

Biliary tract cancer (BTC) is a collective term to include cancers arising from the gallbladder, bile ducts (intra-hepatic, hilar or extra-hepatic cholangiocarcinoma, depending on their site of origin) and ampulla of Vater adenocarcinomas. Although considered relatively rare in the US (with 5000 new cases diagnosed annually [1]) and European countries (e.g. UK incidence: 1200 cases per annum [UK National Statistics homepage at http://www.statistics.gov.uk]), it has a much higher prevalence in Latin America [2] and East Asia. In Japan, the incidence is 10-fold that seen in the West with 17 311 deaths from BTC in 2007 making it the sixth leading cause of cancer death [3]. Moreover, the incidence, particularly of intra-hepatic cholangiocarcinoma, has been increasing in the US, Japan, UK and Australia since the 1970s, [4–6] increasing the need for effective cancer services.

Surgery remains the optimal modality of therapy leading to long-term survival for patients diagnosed with resectable disease. However, most patients have advanced (inoperable or metastatic) disease at presentation, often in the context of biliary obstruction and sepsis and age-related co-morbidities resulting in a 5-year survival of 5%–15% [7, 8].

Two phase III studies have demonstrated improved survival of chemotherapy over best supportive care (BSC) for patients with advanced (inoperable) disease. A Swedish study reported a median survival of 6 months in patients with mixed biliary and pancreatic cancers treated with 5-fluorouracil (5-FU), etoposide and leucovorin chemotherapy compared with 2.5 months with BSC [9]. A study from India in patients with gallbladder cancer demonstrated an improvement in median survival from 4.5 to 9.5 months using a gemcitabine and oxaliplatin regimen [10]. It can be concluded that the median survival in patients treated with

Table 1. Characteristics of the ABC-02 and BT22 trials

Characteristic	Study	
	ABC-02	BT22
Country	UK	Japan
Study design	Randomised phase III	Randomised phase II
Accrual period	February 2002 to October 2008	September 2006 to October 2008
Number of patients	410	84
Key eligibility criteria	Age ≥ 18 years	Age ≥ 20 years
	Confirmed histopathological or cytological diagnosis	Confirmed histopathological diagnosis
	Intra- or extra-hepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma	Intra- or extra-hepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma
	Non-resectable, recurrent or metastatic disease	Non-resectable, recurrent, or metastatic disease
	No prior chemotherapy for advanced disease	No prior chemotherapy for advanced disease
	Performance status of 0–2 (ECOG)	Performance status of 0-1 (ECOG)
	Life expectancy ≥ 3 months	Life expectancy ≥ 3 months
	Total bilirubin level of ≤1.5 × ULN	Total bilirubin level of ≤2 × ULN
	Liver-enzyme levels ≤ 5 × ULN	Liver-enzyme levels ≤ 3 × ULN
	Glomerular filtration rate ≥ 45 ml per minute	Creatinine clearance ≥ 45 ml per minute
Treatment schedule	"CisGem arm": cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2, each on days 1 and 8 of a 21-day regimen	"CisGem arm": cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2, each on days 1 and 8 of a 21-day regimen
	"Gem arm": gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day regimen	"Gem arm": gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day regimen
Duration of treatment	Up to 24 weeks	Until disease progression
Frequency of radiological assessment	Every 12 weeks	Every 8 weeks
Primary end point	Overall survival	1-year survival