法）の3群による第Ⅲ相試験が実施され，GEMに対するGS療法の優越性は証明できなかったものの，S-1の非劣性が確認された．

- これらの臨床試験の結果，切除不能膵癌に対する標準治療としてGEM，S-1，GEM＋エルロチニブ療法が選択可能となっている．FOLFIRINOX療法については現在日本人での有効性と安全性を確認する臨床試験が実施されており，近い将来我が国でも実施が可能となるものと期待される．
- 膵癌の術後補助療法はGEM単独治療が標準治療として確立している．また，我が国でGEMとS-1による非劣性試験が行われ，2012年9月，S-1の非劣性が確認されたとの結果がニュースリリースされた．今後，我が国の術後標準補助療法が変わっていく可能性がある．

最近の重要なstudyとその意義

膵癌でゲムシタビンの有効性が証明

- 本試験は切除不能膵癌を対象としたGEM（63例）と5-FU（63例）のランダム化比較試験である．
- 主要評価項目として疼痛やperformance statusなど臨床症状の改善を目標として実施された．
- 全生存期間中央値はGEM群で5.65カ月，5-FUで4.41カ月（$P=0.0025$）でGEMの有意な生存期間の延長が得られ，膵癌の標準治療薬として確立した．

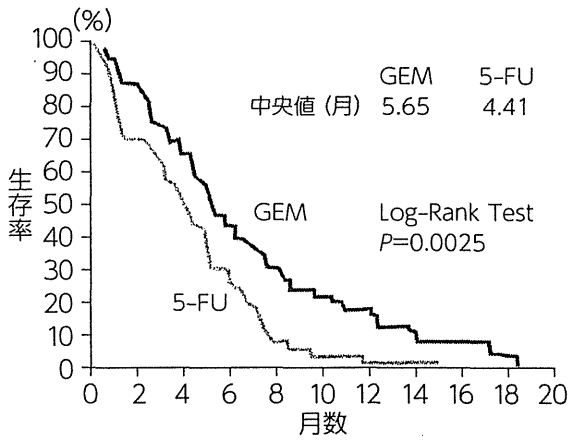

図3　ゲムシタビン vs. 5-FUの全生存率の推移

（文献[1]より改変）

おわりに

- 肝・胆道・膵癌では，この10年の間にそれぞれ標準化学療法が確立し，予後は明らかに改善してきている．特に膵癌では有効な一次治療がいくつか出てきており，今後状況に応じた適切な適応や副作用管理が求められる．
- 一方，これらの疾患は依然予後不良であり，新しい分子標的薬の導入や予後予測因子などバイオマーカーの発現に応じた個別化治療の確立など課題も少なくない．新たな治療法の開発を積極的に進めていくことが必要である．

文　献

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2) Llovet JM, et al：N Engl J Med 359：378, 2008.
3) Valle J, et al：N Engl J Med 362：1273, 2010.
4) Conroy T, et al：N Engl J Med 364：1817, 2011.

What's New in

8 Biliary Tract Cancer 胆道がん

基礎知識

胆道がんは肝外胆道に発症したがん，すなわち胆管がん，胆嚢がん，乳頭部がんが含まれる[1]．肝内胆管がんはUICC分類，わが国の取扱い規約では原発性肝がんに分類されているが，化学療法の臨床試験では胆道がんに含められることも多い．「がんの統計2010」によると，2005年のわが国の胆道がん（胆嚢＋その他および部位不明の胆道の合計）による年間死亡数は17,311人，2004年の罹患数は19,691人である[2]．がん年齢調整罹患率年次推移では1980年代まで増加していたが，それ以降男性は横ばい，女性は減少している[2]．罹患率の国際比較では，胆道がんは日本，東アジア，インド，チリなどで多い．

胆道がんの危険因子として，**胆石や膵液の胆道内逆流などによる胆道への慢性的持続的刺激や炎症**があげられる[3]．具体的には，原発性硬化性胆管炎（PSC），膵・胆管合流異常，胆嚢結石，胆嚢腺筋腫症，肝蛭症などとの関連や化学物質の関与の可能性も報告されている[3~5]．胆嚢結石と胆嚢がんとの因果関係については，胆嚢がんに胆石が合併する頻度は高いが，胆石症の長期経過観察において胆嚢がんの発生頻度が有意に増加するという報告はみられず，直接の因果関係は明らかとなっていない[3]．胆嚢腺筋腫症と胆嚢がんとの関連についても，明らかなrisk factorとされる証拠はない[3]．胆嚢隆起性病変（胆嚢ポリープ）においては，大きさや形状で胆嚢がんとの関連が認められる．**大きさが10 mm以上かつ増大傾向を認める場合，胆嚢壁との付着部の形態が広基性の場合は，胆嚢がんの頻度が高い．**

診　断（各8図-1）

胆道がんにおける高危険群は特定されておらず，特異的な腫瘍マーカーもないことから，胆道がんの検診や無症状でのスクリーニングは難しい．**肝外胆管がんおよび乳頭部がんでは，胆管閉塞による閉塞性黄疸を契機に診断されることが多く**，比較的早期診断が可能である．不定愁訴などを契機に肝胆道系の血液生化学的検査異常を認め，診断されることもある．**胆嚢がんでは特有な症状が少ない**ことから，腹部症状や黄疸などを認める場合は胆嚢がんを念頭においた検査が必要である．

・ファーストステップの検査：血液生化学検査，腫瘍マーカー（CEA, CA19-9），超音波[3]

肝・胆道系酵素や腫瘍マーカーの異常，超音波による胆管拡張，胆嚢壁の異常や隆起性病変，胆管拡張などの異常を認めた場合，精密検査に進む．

・セカンドステップの検査：造影CT，MRI，MRCP，超音波内視鏡（EUS）検査，内視鏡（乳頭部がん）[3]

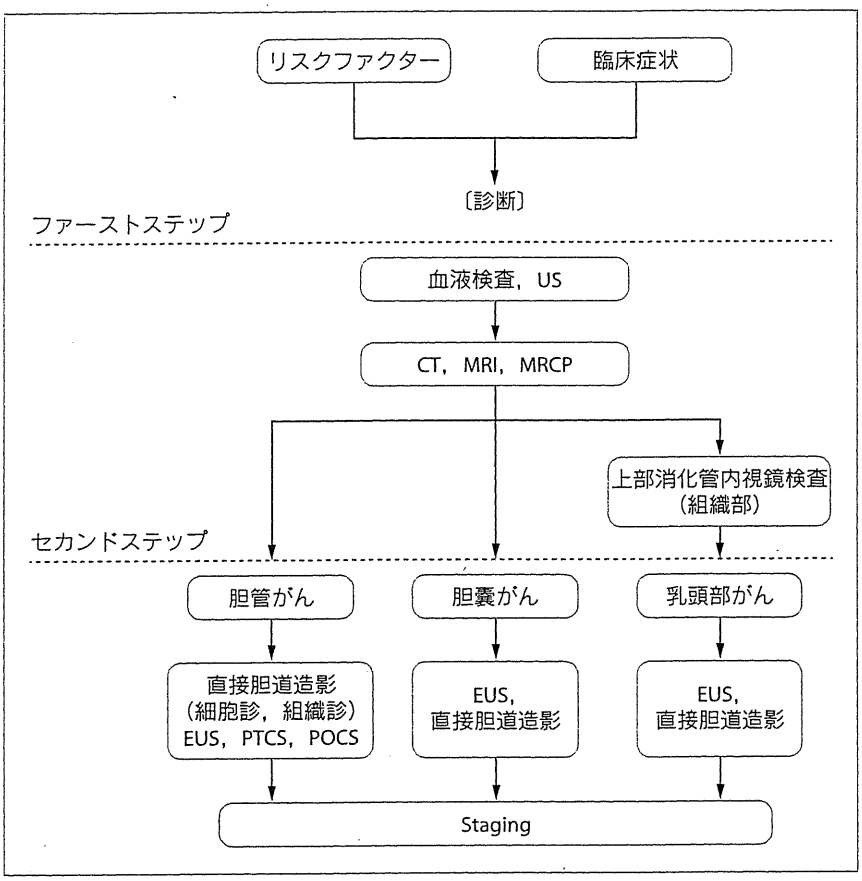
CT，MRIは造影検査が必須であり，胆嚢病変の質的診断に加え，肝など隣接臓器への直接浸潤，肝転移，リンパ節転移の有無など進行度診断に用いられる．MRCPは胆管の閉塞部位，進展範囲の診断，膵・胆管合流異常の確認に用いられる．内視鏡検査では組織生検，細胞診などを行う．

胆道がんの場合，閉塞性黄疸の合併が多く，胆管ドレナージを留置することが多い．切除適応を検討するためには，胆管内のがんの進展範囲を詳細にみることが必要であり，ドレナージを行う前に造影CTを実施する．

Stage（病期）分類・治療方法の選択・予後

Stage分類

胆道癌取扱い規約[1]とUICCのTNM分類[6]が用いられる（各8表-1，2）．胆道癌取扱い規約（第5版）では，手術時の肉眼所見による手術的進行度と，切除標本の最終的組織学的所見による総合的進行度に分類される．非手術症例は手術的進行度に準ずる．



各 8 図-1．胆道がんの診断アルゴリズム
（胆道癌診療ガイドライン作成出版委員会編：エビデンスに基づいた胆道癌診療ガイドライン，医学図書出版，2007）

各 8 表-1．胆道がんの進行度分類

	H_0 P_0 M（−）					H_1，P_1以上 または M（+）
	N_0	N_1	N_2	N_3	N_4	
T1	I					
T2		II				
T3			III	IVa	IVb	
T4						

胆管がんのＴ因子

T1：S_0	$Hinf_0$	$Panc_0$	PV_0	A_0
T2：S_1	$Hinf_1$	$Panc_1$	PV_0	A_0
T3：S_2	$Hinf_2$	$Panc_2$	PV_1	A_1
T4：S_3	$Hinf_3$	$Panc_3$	$PV_{2,3}$	$A_{2,3}$

乳頭部がんのＴ因子

T1：Du_0	$Panc_0$	
T2：Du_1	$Panc_1$	
T3：Du_2	$Panc_2$	
T4：any	$Panc_3$	

胆嚢がんのＴ因子

T1：S_0	$Hinf_0$	$Binf_0$	PV_0	A_0
T2：S_1	$Hinf_1$	$Binf_1$	PV_0	A_0
T3：S_2	$Hinf_2$	$Binf_2$	PV_1	A_1
T4：S_3	any	$Binf_3$	$PV_{2,3}$	$A_{2,3}$

（日本胆道外科研究会編：外科・病理 胆道癌取扱い規約 第 4 版，金原出版，1997）

各 8 表-2. 胆道がんの TNM 分類（UICC 第 7 版，2009 年）

Gallbladder

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III A	T3	N0	M0
Stage III B	T1, T2, T3	N1	M0
Stage IV A	T4	any N	M0
Stage IV B	any T	any N	M1

T1	Lamina propria or muscular layer
T1a	Lamina propria
T1b	Muscular layer
T2	Perimuscular connective tissue
T3	Serosa, one organ and/or liver
T4	Portal vein, hepatic artery, or two or more extrahepatic organs
N1	Along cystic duct, common bile duct, common hepatic artery, portal vein

Extrahepatic bile ducts-Perihilar

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a, T2b	N0	M0
Stage III A	T3	N0	M0
Stage III B	T1, T2, T3	N1	M0
Stage IV A	T4	N0, N1	M0
Stage IV B	any T	any N	M1

T1	Ductal wall
T2a	Beyond ductal wall
T2b	Adjacent hepatic parenchyma
T3	Unilateral branches of portal vein or hepatic artery
T4	Main portal vein ; bilateral branches ; common hepatic artery ; second-order biliary radicals with contralateral portal vein or hepatic artery involvement
N1	Nodes along cystic duct, common bile duct, common hepatic artery, portal vein

Extrahepatic bile ducts-Distal

Stage 0	Tis	N0	M0
Stage I A	T1	N0	M0
Stage I B	T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T1, T2, T3	N1	M0
Stage III	T4	any N	M0
Stage IV	any T	any N	M1

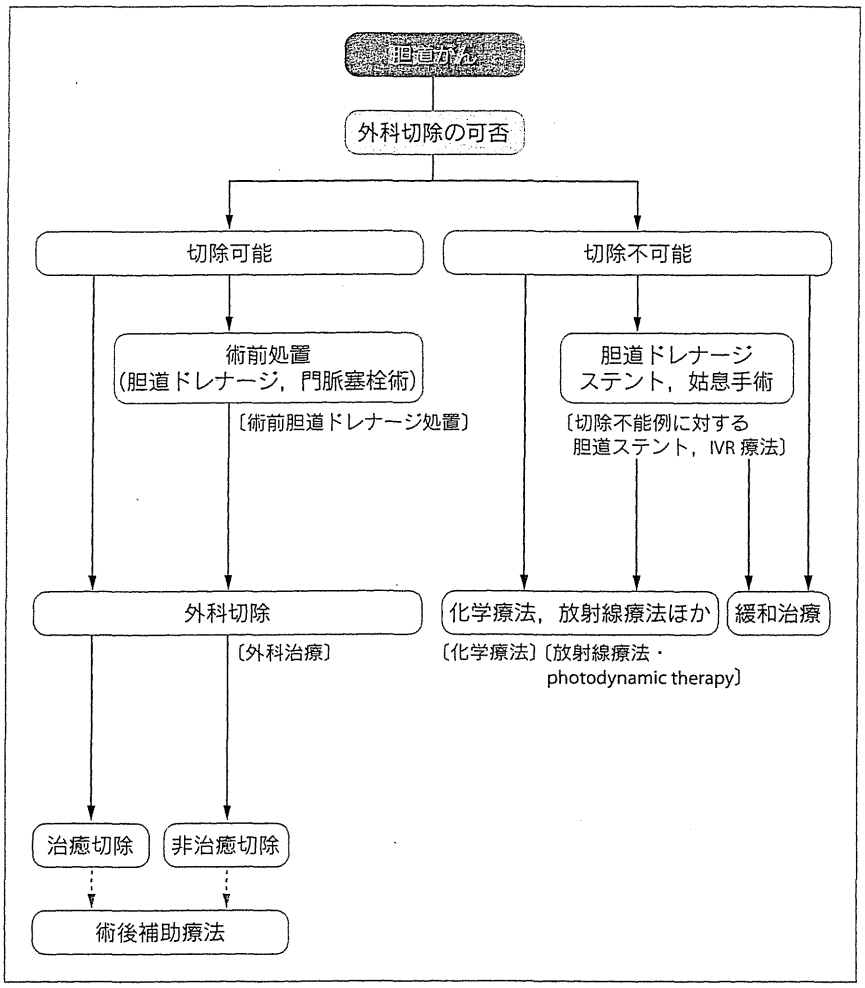
T1	Ductal wall
T2	Beyond ductal wall
T3	Gallbladder, pancreas, duodenum, adjacent organs
T4	Coeliac axis or superior mesenteric artery
N1	Regional

Ampulla of Vater

Stage 0	Tis	N0	M0
Stage I A	T1	N0	M0
Stage I B	T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T1, T2, T3	N1	M0
Stage III	T4	any N	M0
Stage IV	any T	any N	M1

T1	Ampulla or sphincter of Oddi
T2	Duodenal wall
T3	Pancreas
T4	Beyond pancreas
N1	Regional

（文献 6）より）



各 8 図-2．胆道がんの治療アルゴリズム
(胆道癌診療ガイドライン作成出版委員会編：エビデンスに基づいた胆道癌診療ガイドライン，医学図書出版，2007)

治療方法の選択（各 8 図-2）

切除手術が唯一根治を望める治療法であり，切除が第一選択である．切除率は胆嚢がん 69.8%，胆管がん 67%，乳頭部がん 91.2%と比較的高いが，治癒切除率は胆嚢がん 37.7%，胆管がん 30.4%，乳頭部がん 78.5%と胆嚢がん，胆管がんでは根治が難しい傾向にある[7]．切除適応は画像診断，全身状態などから総合的に判断する．切除適応については施設による差も大きく，十分なコンセンサスは得られていない．安易な切除不能の判断は避けるべきである．

切除不能症例では化学療法を考慮する．閉塞性黄疸合併例では十分な減黄後，化学療法の適応を検討する．胆管炎のコントロールが困難，全身状態不良，重篤な合併症を伴うなどの場合化学療法は適応外であり，緩和治療に専念する．

放射線療法については，これまで大規模な比較試験による検証は行われていない．遠隔転移のない局所進行の胆管がん（特に肝門部胆管がん）では放射線療法に良好な局所コントロールが報告されているが，治療効果には限界があるとの報告もある[8~10]．

予　後

根治切除が行われ，リンパ節転移なし，神経周囲浸潤なし，TNM Stage I などの早期例では良好な予後が報告されている[11~16]．胆管がん，胆嚢がん，乳頭部がんに共通した切除後予後因子として，リンパ節転移および神経周囲浸潤の有無があげられる[3]．その他，胆管がんでは治癒切除の有無，門脈・肝動脈への浸潤による血管合併切除の有無，胆嚢がんでは UICC TNM-Stage，壁深達度，肝外胆管浸潤，肝床浸潤，肝十二指

各 8 表-3．多施設共同後ろ向き解析による胆道がん化学療法の治療成績

	n	奏効率	生存期間中央値	1 年生存率
肝内胆管がん	54	5.6%	8.7 カ月	34.3%
肝外胆管がん	37	5.4%	10.1 カ月	39.6%
胆嚢がん	102	10.8%	6.5 カ月	16.9%
乳頭部がん	14	21.4%	9.3 カ月	45.7%
全　体	207	9.2%	7.7 カ月	28.4%

（文献 17）より）

腸間膜浸潤，組織型，根治度，乳頭部がんでは膵浸潤の有無，などが報告されている[11~16]．

切除不能例の予後は，化学療法の後ろ向き調査によると，生存期間中央値（MST）7.7 カ月程度であり，疾患別では胆嚢がんで有意に予後不良である（各 8 表-3）[17]．最近行われた gemcitabine（GEM）と GEM＋cisplatin（GC）併用療法による比較試験では，MST は GC 療法 11～12 カ月群，GEM 群 8 カ月程度と報告されている[18,19]．

治療方法

切除術

切除適応は全身状態，腫瘍の局所進展，転移（リンパ節，肝，腹膜，肺ほか）の評価によって決定される．胆道癌診療ガイドラインでは，切除不能の腫瘍の局所進展について，Jarnagin らによる肝門部胆管がんの T-Stage 分類から局所進展因子を次の①～⑤のように規定しているが，門脈・肝動脈合併切除や広範囲肝切除なども行われており，十分なコンセンサスが得られているとはいえないとしている[3,20]．

①両側胆管 2 次分岐までの浸潤
②門脈本幹の狭窄または閉塞（門脈分岐部の近位部）
③肝片葉の萎縮と対側門脈枝の狭窄または閉塞
④肝片葉の萎縮と対側の胆管 2 次分岐までの浸潤
⑤片側胆管 2 次分岐までの浸潤と対側門脈枝の狭窄または閉塞

リンパ節転移についても十分なコンセンサスが得られていないが，画像上明らかな大動脈周囲リンパ節転移が認められる場合は切除不能である[16]．両側肝動脈浸潤，遠隔転移を認める場合も，切除適応はない．

術後補助療法については大規模な臨床試験は行われておらず，十分なエビデンスは確立していない．唯一，mitomycin C＋fluorouracil 併用療法（MF 群）と切除単独群による比較試験が行われ[21]，胆嚢がんで予後の改善を認めているが，非治癒切除例に限られること，ITT では有意差を認めていないこと，MF 療法が普及していないことから，標準治療として位置づけられていない．現在，日本では胆管がんを対象として GEM と切除単独，英国では胆道がんを対象として capecitabine と切除単独の無作為化比較試験が施行されており，その結果を待つ必要がある．さらに，胆道がん全体を対象に tegafur・gimeracil・oteracil potassium（TS-1）配合薬や GEM＋cisplatin（CDDP）併用療法などを用いた臨床試験も進められている．

胆管がんにおいて断端陽性例では追加切除を行うが，術後最終病理診断でも断端陽性となった場合の治療についても標準的な方法は確立していない．胆管上皮のみの遺残の場合は予後への影響はほとんどなく，そのまま経過をみる[22]．壁内の遺残に対しては施設によって対応が異なり，放射線療法を行う施設，化学療法を行う施設などさまざまであり，一定の見解もないし，エビデンスもない．

放射線治療

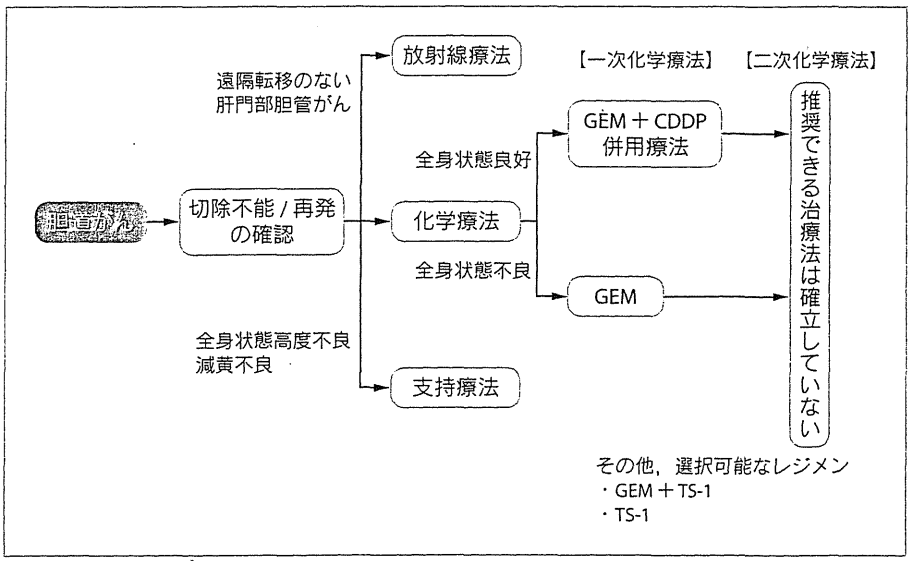
局所進展による切除不能胆管がんでは化学放射線療法，特に体外照射と腔内照射の併用療法で良好な局所コントロールが報告されているが[8~10]，これまで大規模な無作為化比較試験は行われておらず，放射線療法の有効性に関するエビデンスは確立していない．

化学療法

胆道がんにおける化学療法の臨床的意義，すなわち延命効果の有無については，化学療法と無治療（支持

各 8 表-4. 胆道がんにおける化学療法の主な適応基準

①画像診断を含めた臨床診断上胆道がんと診断され，組織診または細胞診により確認されていること．
②切除適応がないこと．
③ECOG performance status が 0〜2．
④主要臓器（骨髄，肝，腎など）の機能が十分に保持されていること．
⑤閉塞性黄疸合併例では減黄が行われていること．
⑥活動性の急性感染症がないこと．特に胆管炎が十分制御されていること．
⑦重篤な合併症（急性期の心疾患や脳疾患，心不全，腎不全，肝不全，活動性の消化性潰瘍，腸管麻痺，コントロール不良な糖尿病など）がないこと．
⑧少なくとも 2 カ月以上の生存が期待できること．
⑨本人から文書にて同意が得られていること．
⑩該当薬剤の適応禁忌に抵触しないこと．



各 8 図-3. 切除不能胆道がんの治療選択
GEM：gemcitabine　CDDP：cisplatin

療法）との小規模な無作為化試験が報告されている[23,24]．化学療法として，fluorouracil（5-FU）＋leucovorin（LV）あるいは 5-FU＋LV＋etoposide が用いられている．全対象で支持療法群〔生存期間中央値（MST）2.5 カ月〕に比べ化学療法群（MST 6.0 カ月）で有意に生存期間の延長が認められた（$p<0.01$）．しかし，胆道がん患者に限ると 37 例と症例数が少なく，両群に有意差は認められていない（化学療法群 MST 6.5 カ月，支持療法群 2.5 カ月，$p=0.1$）．この試験では QOL の改善についても検討されており，化学療法群での QOL 改善率 36%（膵がん 38%，胆道がん 33%），支持療法群での改善率 10%（膵がん 13%，胆道がん 5%）と化学療法群で有意に QOL の改善が認められている（$p<0.01$）．

最近，胆嚢がん患者を対象とした支持療法と 5-FU＋LV あるいは GEM/oxaliplatin（Gemox 療法）の化学療法の比較試験が報告された[24]．支持療法（n＝27），5-FU＋LV（n＝28），Gemox（n＝26）の MST はそれぞれ 4.5 カ月，4.6 カ月，9.5 カ月と，支持療法，5-FU＋LV では差は認めなかったが，Gemox 療法で有意に生存期間の改善が得られている．

化学療法の適応は，切除不能の局所進行や遠隔転移を有する例，あるいは切除後の再発例に限られる（各 8 表-4）．全身状態の低下した例や減黄不良例などでは化学療法の利益は少ない．このような患者では，疼痛コントロール，閉塞性黄疸に対する胆管内ステントの留置など QOL の維持を目指した緩和治療を行う（各 8 図-3）．

切除不能胆道がんにおける化学療法は，主に GEM を基本薬剤としてフッ化ピリミジン系薬，プラチナ系薬などの薬剤との併用療法が試みられてきた．わが国では GEM 単独と TS-1 単独の単アームによる第Ⅱ相試験（治験）により良好な成績が得られ[25,26]，保険適応が承認されている．胆道癌診療ガイドラインでは，GEM あるいは TS-1 が切除不能胆道がんに対する化学療法として推奨されているが，大規模な比較試験による検証は行われていなかった．

各8表-5．進行胆道がんに対するGEMとGEM＋CDDP併用療法の無作為化比較試験

	ABC-02試験		BT-22試験	
	GEM	GEM＋CDDP	GEM	GEM＋CDDP
N	206	204	42	41
原発巣				
肝外胆管がん	119（57.8%）	122（59.8%）	11（26.2%）	8（19.5%）
肝内胆管がん			14（33.3%）	14（34.1%）
胆嚢がん	76（36.9%）	73（35.8%）	17（40.5%）	15（36.6%）
乳頭部がん	11（5.3%）	9（4.4%）	0	4（9.8%）
奏効率	15.5%	26.1%	11.9%	19.5%
病勢コントロール率	71.8%	81.4%	50.0%	68.3%
PFS	5.0カ月	8.0カ月*1	3.7カ月	5.8カ月
MST	8.1カ月	11.7カ月*2	7.7カ月	11.2カ月

*1：ハザード比0.63（95% CI：0.51～0.77），p<0.001
*2：ハザード比0.64（95% CI：0.52～0.80），p<0.001
GEM：gemcitabine, CDDP：cisplatin

英国で行われたGEM単独とGEM＋CDDP併用（GC療法）の無作為化第Ⅱ相試験（ABC-01試験）において，GEM単独群の奏効率15%，無増悪生存期間中央値（PFS）4カ月に対し，GC療法群ではそれぞれ24%，8カ月とGC療法の有用性が示唆され[27]，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（各8表-5）[18]．わが国でもABC-02試験と同様のレジメンで無作為化比較試験（BT-22試験）が行われ，ほぼ同じ結果が得られている（各8表-5）[19]．

【主な化学療法レジメン】（各8図-4）

① GEM＋CDDP併用療法

・GEMとの比較試験により，奏効率20～26%，MST 4.6～11.0カ月の成績が得られている．
・保険適応承認：2012年2月
・投与法（各8図-4-1)）：GEMは通常の1,000 mg/m^2，30分点滴静注であるが，CDDPは25 mg/m^{2}と低用量の投与法が用いられている．
・主な有害反応：GEMに加え，CDDPの副作用にも注意が必要である．比較試験では，GEM単独に比べ頻度の高い副作用は骨髄抑制，悪心・嘔吐であったが，重篤なものはほとんどなかった[18,19]．

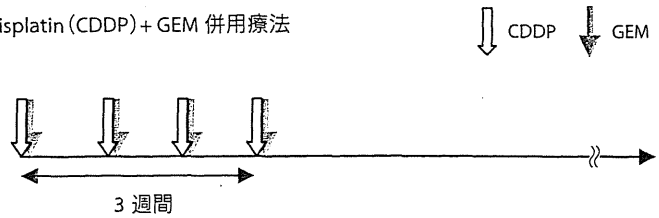
② GEM単独療法

・わが国で実施された第Ⅱ相試験（n＝40）[24]：奏効率17.5%，MST 7.6カ月，無増悪生存期間中央値（PFS）2.6カ月
・保険適応承認：2006年6月
・投与法（各8図-4-2)）：1,000 mg/m^2，30分で点滴静注，週1回，3週投与，1回休薬，4週毎に繰り返す．
・主な有害反応：骨髄抑制，食欲不振，悪心・嘔吐，ALT上昇，発熱，疲労感，AST上昇など．重篤な副作用は骨髄抑制に起因する敗血症，間質性肺炎（1.5%），アナフィラキシー様症状（0.3%），心筋梗塞（0.3%），うっ血性心不全，肺水腫，気管支痙攣，成人呼吸促迫症候群，腎不全，溶血性尿毒症症候群など．

③ tegafur・gimeracil・oteracil potassium配合薬（TS-1）単独療法

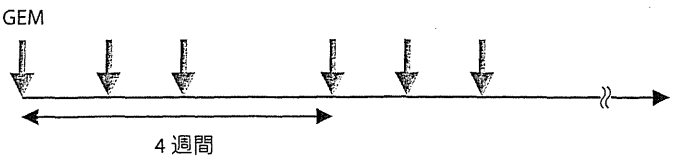
・多施設共同後期第Ⅱ相試験25)：奏効率32.5%，MST 9.4カ月，PFS 3.7カ月
・保険適応承認：2007年8月
・投与法（各8図-4-3)）：80 mg/m^2（S<1.25 m^2：80 mg，1.25≦S<1.5 m^2：100 mg，S≧1.5 m^2：120 mg/body/day），朝夕分2内服，第1～28日内服，第29～42日休薬，6週毎に繰り返す．
・主な有害反応：骨髄抑制，食欲不振，悪心・嘔吐，下痢，口内炎，色素沈着，発疹など．重篤な副作用は骨髄抑制，溶血性貧血，劇症肝炎などの重篤な肝障害，脱水，腸炎（0.2%），間質性肺炎（0.4%），口内炎，消化管潰瘍，消化管出血，急性腎不全，皮膚粘膜眼症候群，中毒性表皮壊死症，嗅覚消失など．

1) cisplatin (CDDP) + GEM 併用療法



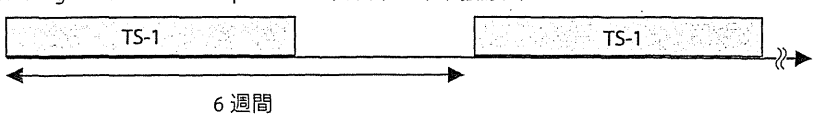
① CDDP : 25mg/m², 60 分で点滴静注
② GEM : 1,000 mg/m², 30 分で点滴静注
①, ②を週 1 回, 2 週投与, 1 回休薬, 3 週毎に繰り返す

2) gemcitabine (GEM) 単独療法



1,000 mg/m², 30 分で点滴静注, 週 1 回, 3 週投与, 1 回休薬,
4 週毎に繰り返す

3) tegafur・gimeracil・oteracil potassium 配合 (TS-1) 単独療法



80mg/m²(S < 1.25m² : 80mg, 1.25 ≤ S < 1.5m² : 100mg, S ≥ 1.5m² : 120mg/body/day)
朝夕分 2 内服, 第 1～28 日内服, 第 29～42 日休薬, 6 週毎に繰り返す

【レジメン例】

メインルート：	生理食塩液 1,000mL	3 時間点滴静注
側 管：		
①	生理食塩液 100mL + dexamethasone 6.6～9.9mg	30 分点滴静注
②	生理食塩液 100mL + 5-HT_3 受容体拮抗薬 1A	30 分点滴静注
③	CDDP 25mg/m²	1 時間点滴静注
④	生理食塩液 100mL + GEM 1,000mg/m²	30 分点滴静注

各 8 図-4. 胆道がんの主な化学療法レジメン

胆道ドレナージ

胆道がん切除術では, 術前減黄については, 閉塞性黄疸では肝機能をはじめ多臓器にわたる障害を引き起こす可能性があり, 従来胆道ドレナージが行われてきた. しかし, 欧米で行われた無作為化比較試験により術後の合併症発生率, 死亡率に差がないとの報告から必要ないとの考えもある[29]. 一方, 最近ではドレナージの安全性は高く, 減黄のデメリットは少なくなっている. 高度黄疸例, 胆管炎併発, 肝機能低下例, 広範囲肝切除など侵襲の大きな手術例では基本的に減黄が必要である.

切除不能例に対する減黄は, 化学療法や放射線療法では必須である. 緩和治療のみの場合は, 閉塞性黄疸に起因する症状に応じて実施する. 胆道ドレナージの方法は, 内視鏡的アプローチと経皮経肝的アプローチが行わ

各 8 表-6. 胆道がんの Stage 別治療方針

Stage (UICC)	治療方法・レジメン	文献
0	切除	3, 20)
ⅠA	切除	3, 20)
ⅠB	切除	3, 20)
ⅡA	切除	3, 20)
ⅡB	切除＞全身化学療法：GEM＋CDDP，放射線療法*	3, 10, 20)
Ⅲ	切除＞全身化学療法：GEM＋CDDP，放射線療法*	3, 10, 20)
Ⅳ	全身化学療法：GEM＋CDDP	18, 19)

GEM：gemcitabine，CDDP：cisplatin
＊：放射線療法：胆管がんの Stage ⅡA，B，Ⅲで切除不能の場合に選択肢となる．

れているが，一般的には内視鏡的アプローチが優先されている．どちらでも確実に胆管内にドレナージチューブを留置する．胆嚢へのドレナージは有効な減黄ができないこと，胆管炎のリスクが高いことなどのため避ける．

以前は 8～10 Fr のプラスチックステント（特に ERBD）が用いられていたが，内径が狭く早期閉塞が必発であった．最近ではメタリックステント（径 6～10 mm）により長期開存も可能となり，開存期間ではプラスチックステントより優れていることが報告されている[29,30]．メタリックステントはメッシュ構造の uncovered type とポリウレタンでカバーされた covered type がある．膵がん，胆道がん，リンパ節転移による肝外閉塞 112 例を対象とした両者の無作為化比較試験が行われ，早期合併症は covered type で急性胆嚢炎 4.8%，膵炎 8.7%を認めたのに対し，uncovered type では胆嚢炎は認めず，膵炎 1.8%，胆道出血 3.6%認めたと報告されている[31]．また，平均生存期間は covered type 255 日，uncovered type 237 日と差は認めなかったが，平均ステント開存期間は covered type 304 日，uncovered type 161 日と有意に covered type で良好であった（p＝0.0354）．肝外胆管の閉塞では目詰まりなどが起きにくい covered type が有用である．肝門部の泣き別れ胆管閉塞ではメッシュの uncovered が適当であり，閉塞に合わせた複雑な挿入を行うため技術の十分な習熟が必要である．患者の QOL を考慮し，可能な限りステントによる内瘻化を図る．

【ドレナージの種類と適応】

- 経鼻的ドレナージ（endoscopic naso－biliary drainage：ENBD）：緊急かつテンポラリーなドレナージ．
- 内視鏡的ドレナージ（endoscopic retrograde biliary drainage：ERBD）：簡便に実施可能．消化管狭窄例では困難．
- 経皮経肝的ドレナージ（percutaneous transhepatic cholangio drainage：PTCD/percutaneous transhepatic biliary drainage：PTBD）：肝門部胆管がんなど左右胆管あるいは末梢胆管の泣き別れ閉塞では必須．

最新の動向

切除不能胆道がんに対する標準治療は一次治療として，海外では GC 療法に加え，GEM＋oxaliplatin 併用療法（Gemox 療法）が多く用いられている．インドでも，小規模な比較試験ではあるが，支持療法のみに比べ，Gemox 療法の延命効果が報告されている[32]．わが国では JCOG（日本臨床腫瘍研究グループ）試験として，TS-1 と GEM＋TS-1 併用療法（GS 療法）の無作為化比較試験が行われ[33]，GS 療法の有用性が示唆されたことから，今後 GC 療法と GS 療法の第Ⅲ相試験が検討されている．

分子標的薬として，抗 EGFR 抗体薬 cetuximab，panitumumab が Gemox 療法（Gemox＋capeciatbine）への上乗せがフランスなど欧州で試みられている．イタリアでは EGFR，VEGFR 阻害薬と GEM 併用療法の無作為化第Ⅱ相試験が，また英国では GC 療法＋VEGFR 阻害薬 cediranib の無作為化第Ⅱ相試験が実施されている．わが国では，GC 療法に Wilms 腫瘍遺伝子 WT1 に対するペプチドワクチンの併用治療の無作為化第Ⅱ相試験が開始されている．

術後補助療法については，わが国では手術単独と GEM との比較試験（BCAT 試験）が実施され，すでに登録が終了している．また，TS-1 は第Ⅱ相試験で 30%を超す高い奏効割合が得られていることから，TS-1 を用いた術後補助療法の比較試験が計画されている．英国では capecitabine による手術単独との比較試験が

実施中である．このように，いくつかの手術単独との比較試験が実施されつつあり，近い将来，標準的術後補助療法が確立するものと期待される．

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A Retrospective Study of S-1 Monotherapy as Second-line Treatment for Patients with Advanced Biliary Tract Cancer

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Objective: Gemcitabine has been widely used, and cisplatin plus gemcitabine is considered as standard first-line chemotherapy for patients with advanced biliary tract cancer. However, no standard therapy was established following the progression to gemcitabine-containing first-line therapy. As S-1 monotherapy as second-line chemotherapy is still not well known in a practical setting this study aimed to clarify its efficacy and safety.
Methods: We retrospectively reviewed 55 consecutive patients who received S-1 monotherapy as second-line chemotherapy after failure of a gemcitabine-containing regimen at our institution from September 2007 to March 2011. The inclusion criteria were preserved organ function and an Eastern Cooperative Oncology Group performance status of 0–2 and without massive ascites or pleural effusion. S-1 was administered orally twice a day at a dose of 40 mg/m^2 for 28 days, followed by 14 days of rest.
Results: Fifty-one patients were selected for this analysis. The overall response rate was 4.0% and the disease control rate was 38.0%. The median survival time was 6.0 months and the median progression-free survival was 2.3 months. Adverse events were generally mild, and treatment-related death did not occur. In the subgroup analysis, overall survival was significantly shorter in the patients with peritoneal dissemination and those who had shown no response to the first-line chemotherapy ($P = 0.033$ and 0.023, respectively).
Conclusions: S-1 monotherapy as the second-line chemotherapy for patients with gemcitabine-refractory advanced biliary tract cancer is also feasible in a practical setting and its efficacy is almost the same as in the previous prospective study.

Key words: S-1 – biliary tract cancer – second-line – gemcitabine refractory

INTRODUCTION

Biliary tract refers to all routes that bile juice passes through from hepatocytes to the duodenum, including intrahepatic bile duct, extrahepatic bile duct, gall bladder and ampulla of Vater. Therefore, biliary tract cancer (BTC) includes intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder carcinoma and ampullary carcinoma. Sometimes, intrahepatic cholangiocarcinoma is classified as primary liver cancer by UICC (1) and Japanese classification (2), but it is more often classified as BTC because of its development, as well as pathological and clinical features.

BTC is not a common disease throughout the world; however, it is more commonly encountered in East Asia and Latin America than any other countries (3). Furthermore, it is the sixth leading cause of cancer-related death in Japan.

They are usually found in unresectable stage; however, resection surgery is the only way to cure BTC. Moreover, recurrence after curative surgery is common because BTC has high malignant potential and propensity to metastasize. Therefore, systemic chemotherapy is important for the treatment of BTC. Gemcitabine (GEM) has shown efficacy and safety for advanced BTC in many reports (4–6). GEM is considered the key drug for the treatment of advanced BTC, and GEM monotherapy was recognized as a community standard in Japan until 2010. In 2010, the results of the Phase III study of cisplatin (CDDP) plus GEM versus GEM for advanced BTC were reported (7) and GEM and CDDP combination therapy showed superiority to GEM monotherapy. Similar results were also reported in Japanese Phase II study (8). CDDP and GEM combination therapy is now considered as a standard first-line regimen for advanced BTC. In 2011, CDDP received approval from social insurance in Japan for advanced BTC.

No standard therapy was established following the progression to GEM-containing first-line therapy. S-1 is an oral agent consisting of a mixture of tegafur, 5-chloro-2, 4-dihydroxypyrimidine and potassium oxonate at a molar ratio of 1:0.4:1 (9), which has mainly been investigated in Asian countries. In a Phase II study of S-1 as a drug for first-line chemotherapy for advanced BTC, it was reported that the objective response rate was 32.5%, and the median survival time (MST) was 9.4 months with median time to progression (TTP) 3.7 months (10,11). Because of the good anti-tumor activity, two prospective studies of S-1 monotherapy as second-line therapy after the progression to GEM (12,13) were conducted. In these studies, the objective response rates were 22.7 and 7.5% and the values of MST were 13.5 and 7.5 months. S-1 is practically used as a drug for second-line chemotherapy in Japan to treat advanced BTC.

However, these results were quite different from one another. Consequently, the efficacy and safety of S-1 monotherapy as second-line therapy for advanced BTC is still not established in a practical setting, which is why we performed this retrospective analysis.

PATIENTS AND METHODS

Patients

The subjects were 55 consecutive patients who received S-1 monotherapy as second-line chemotherapy after the failure to GEM-containing regimen at Kanagawa Cancer Center between September 2007 and March 2011. We retrospectively reviewed their medical records. All the patients received a pathological and graphical diagnosis of BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary carcinoma). Advanced BTC was defined as (i) metastasis to other organs or to a distant lymph node, (ii) metastasis to form a bulky lymph node of hepatoduodenal ligament, (iii) invasion to common hepatic artery or proper hepatic artery or celiac artery or superior mesenteric artery, (iv) invasion to the bilateral branches of hepatic artery, (v) invasion to the trunk of portal vein which leads to the growth of collateral vessels, or invasion to the bilateral branches of portal vein, (vi) invasion to the bilateral secondary branch of the bile duct, (vii) invasion to one side of the hepatic artery/portal vein and invasion to another side of the secondary branches of the bile duct and (viii) recurrence after curative surgery. In addition to these criteria, intrahepatic cholangiocarcinoma with intrahepatic metastasis in the bilateral lobe is also defined as advanced BTC. Additional criteria for this retrospective analysis included an Eastern Cooperative Oncology Group performance status (PS) of 0–2, good bone marrow function, white blood cell count $\geq 3000/mm^3$, neutrophil count $\geq 1500/mm^3$, hemoglobin ≥ 8.5 g/dl, platelet count $\geq 100\,000/mm^3$, good renal function (serum creatinine ≤ 1.5 mg/dl) and good liver function (total bilirubin ≤ 2.0 mg/dl and transaminase levels ≤ 2.5 times the upper limit of the normal ranges). Patients with obstructive jaundice were eligible after receiving adequate biliary drainage and decreasing transaminase levels (less than five times the upper limit of the normal range). Patients were excluded if they had not received GEM in the first-line regimen or had already received S-1, or if they had massive ascites, pleural effusion, active concomitant malignancy, brain metastasis, interstitial pneumonia, uncontrolled diabetes mellitus and regular use of warfarin, phenytoin or frucitocin.

Treatment

S-1 was administered orally twice a day at a dose of 40 mg/m^2. The initial doses were determined according to the body surface area (BSA) calculated by body weight and height as follows: BSA $< 1.25\ m^2$, 80 mg/day; $1.25\ m^2 \leq$ BSA $< 1.5\ m^2$, 100 mg/day; $1.5\ m^2 \leq$ BSA, 120 mg/day. S-1 was given for 28 days followed by 14 days of rest. Dose reduction and interruption were considered in the case of severe toxicities (graded as 3–4) according to the Common Terminology Criteria of Adverse Event version 4.0 (CTCAE v4.0). No dose re-escalation was conducted following the dose reduction. This treatment course was repeated until disease progression, unacceptable toxicities or patients' refusal.

Evaluation

Tumor response was assessed approximately every 2 months in contrast-enhanced computed tomography according to the Response Evaluation Criteria In Solid Tumor (RECIST, version 1.1). Toxicities were evaluated according to the CTCAE v4.0. Overall survival was defined as the duration from the date of treatment initiation to the date of death of any cause or the last follow-up. Progression-free survival (PFS) was defined as the duration from the date of S-1 treatment initiation to the date of documented disease progression

or death. The overall survival and PFS were calculated using the Kaplan–Meier method. Subgroup analyses were evaluated with the log-rank test and the Cox proportional hazard model. This study was approved by Kanagawa Cancer Center institutional review board.

RESULTS

Subjects

One hundred and thirteen patients with advanced BTC received GEM monotherapy or GEM plus CDDP combination therapy as the first-line treatment and 83 patients discontinued. Among these 83 patients, 55 patients received S-1 monotherapy as the second-line treatment and 51 patients were selected for this study according to the eligibility criteria. The reason for exclusion was anemia due to the first-line treatment in one patient, massive ascites in one patient, PS 3 in one patient and patient's refusal for surgical treatment in one patient. The patient characteristics are shown in Table 1. Among the 51 patients, the median age was 69 years (range 39–81), 29 (57%) were male and all the patients except only one had an Eastern Cooperative Oncology Group PS of 0–1. The number of patients with gallbladder carcinoma was 26 (51%), and that with recurrent disease after the curative surgery was 8 (16%). Regarding the first-line treatment, the number of patients who had received GEM monotherapy was 47 (92%), while the number of patients who received GEM plus CDDP combination therapy was 4 (8%). In GEM monotherapy and GEM plus CDDP combination therapy, PFS was 4.0 and 3.4 months, 5 patients (10.6%) and 1 (25%) patient showed a partial response and 26 (55.3%) and 2 (50%) showed stable disease, respectively.

Treatment

A total of 176 courses were administered, with a median of two courses per patient (range 1–18). Dose reduction due to the adverse events was conducted in 17 (33%) patients, and treatment was interrupted during the course in 15 (29%) patients. The median dose intensity of S-1 was 87.3% (range 38.4–100%) compared with the planned dosage. S-1 monotherapy was discontinued in 43 (84%) patients because of the disease progression and in 4 (8%) patients because of the adverse events (Grade 2 nausea in two patients, Grade 2 gastrointestinal bleeding in one and Grade 2 anorexia in one). Four patients (8%) had been receiving S-1 monotherapy at the time of this analysis.

Efficacy

Excluding 1 patient who could not be evaluated, 2 (4.0%) patients showed partial responses and 19 (38%) showed stable disease, resulting in an overall objective response rate of 4% and a disease control rate of 42%. The overall MST was 6.0 months and the PFS was 2.3 months (Fig. 1). In subgroup analysis according to the presence of ascites, indicating the presence of peritoneal dissemination, the MSTs of patients with and without ascites were 2.2 and 6.8 months ($P = 0.033$), respectively. And there was a significant difference in overall survival between patients who had progressive disease against the first-line chemotherapy and who had any response (3.5 and 7.2 months, respectively, $P = 0.023$). These two factors were also significant in multivariate analysis; the hazard ratios were 3.2 and 2.3, respectively. However, there was no significant difference between gallbladder carcinoma and non-gallbladder carcinoma (Table 2).

Toxicities

Table 3 presents the adverse events that occurred during the S-1 monotherapy as the second-line treatment. No treatment

Table 1. Patient characteristics

	Patients ($n = 51$)	Percent
Median age (range)	69 (39–81)	
Gender		
Male	29	56.9
Female	22	43.1
ECOG PS		
0	40	78.4
1	10	19.6
2	1	2.0
Location of primary tumor		
Intrahepatic bile duct	15	29.4
Extrahepatic bile duct	9	17.6
Gallbladder	26	51.0
Ampulla of Vater	1	2.0
Extent of disease		
Local advanced	16	31.4
Metastatic (prior curative surgery)	35 (8)	68.6 (15.7)
With ascites	5	9.8
CEA before treatment (ng/ml)		
≤5.0	22	43.1
>5.0	29	56.9
CA19-9 before treatment (mU/ml)		
≤37	13	25.5
>37	38	74.5
Prior treatment regimen		
Gemcitabine alone	47	92.2
Gemcitabine + cisplatin	4	7.8

ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

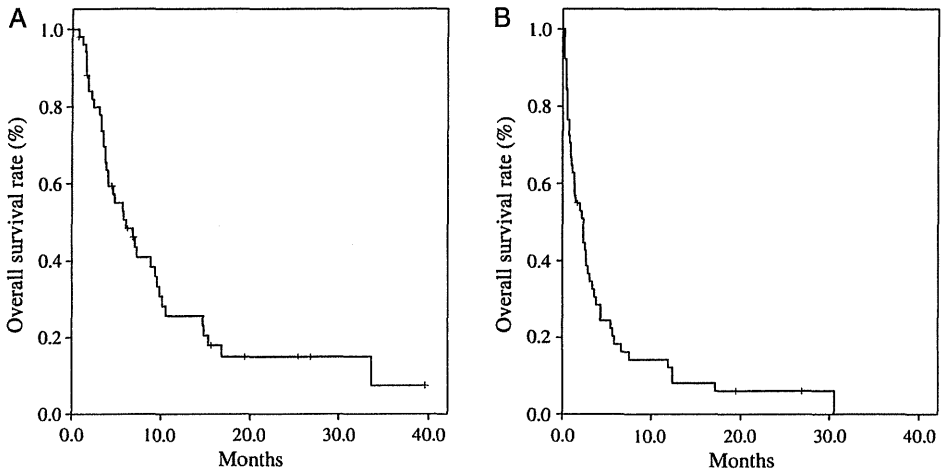

Figure 1. (A) The Kaplan–Meier curves for overall survival. The median survival time was 6.0 months [95% confidence interval (CI): 3.4–8.6]. (B) The Kaplan–Meier curves for progression-free survival (PFS). The median PFS was 2.3 months (95% CI: 1.2–3.4).

death occurred, and generally, toxicities were mild: Grade 3/4 hematologic adverse events, which include anemia, leukopenia, neutropenia and thrombocytopenia, were observed in only one patient for each, and non-hematologic adverse events with Grade 3/4 were diarrhea (three patients, 6%), anorexia (one patient, 2%), nausea (one patient, 2%), mucositis oral (one patient, 2%) and rash (one patient, 2%).

DISCUSSION

In this analysis, ~64% of the patients received second-line chemotherapy after being refractory to GEM-containing regimen similar to 70% of the patients who received the second-line chemotherapy in the past study (8). These findings indicate that the development of effective second-line chemotherapy is critical to the treatment of advanced BTC. However, there is no standard regimen after the refractory condition to the GEM plus CDDP regimen, as National Comprehensive Cancer Network guideline shows no recommendation about it.

5-Fluorouracil (5-FU) was expected to have an anti-tumor effect for advanced BTC, and some studies of 5-FU monotherapy or 5-FU combination regimen as first-line treatment were reported previously (14–19). According to these studies, it is considered that 5-FU was ineffective as an agent for first-line treatment. S-1, which is a 5-FU derivative, is a promising agent for first-line treatment (10,11). However, the agent effective in the first-line treatment is not always effective in the second-line treatment, and it is necessary to evaluate the efficacy and safety of the agent in the second-line treatment. The results of the current study were similar to the report published by Suzuki et al. (13) at the 2010 annual meeting of the American Society of Clinical Oncology. On the other hand, the results reported by Sasaki et al. (12) were largely better than those of the current study. One of the reasons for the difference may be the patient's characteristics, especially the primary site of tumor and peritoneal dissemination. It was reported that gallbladder cancer has a poor prognosis (6,20). Gallbladder cancer was included 51% in the current study, while only 27% in the Phase II study reported by Sasaki et al. (12). As for the peritoneal dissemination, it was not mentioned in the report so it cannot be compared. Instead, they insisted on the tumor volume rather than on the primary site. From this point of view, patients with recurrent disease show better prognosis than those with non-resectable disease because careful observation results in small tumor volume when the recurrence is pointed out (8). However, no survival difference was observed between the patients with recurrent disease and non-resectable disease in our study, and since the outcome that recurrent case had better prognosis may mean lead time bias, further studies are needed to address this issue.

Subgroup analysis of our study indicates that patients who had shown progressive disease for the first-line chemotherapy administering GEM tended to have worse prognosis despite the second-line chemotherapy of S-1 than those who had shown disease control. It means that S-1 monotherapy as second-line treatment may not salvage patients who did not show any response to the GEM-containing regimen. Neither GEM nor CDDP cross-reacts with S-1 in pharmacokinetics (21–25), and patients who showed disease progression against both first-line and second-line chemotherapy may have other complex factors. Nonetheless, it is important to exercise caution while interpreting the results of this retrospective study, as the patients' backgrounds are different from one another.

Concerning the toxicities, Grade 3–4 adverse events were not frequent and no treatment-related death was observed. Moreover, treatment discontinuation was needed for only four (8%) patients. Therefore, two prospective studies and the current study showed similar results, indicating that S-1 monotherapy is tolerable in the second-line treatment after the GEM failure.

Table 2. Prognostic factors for overall survival

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender				
Male	1			
Female	0.82 (0.43–1.57)	NS		
Age ≤65 years old				
Yes	1			
No	1.46 (0.76–2.80)	NS		
Performance status				
0	1			
1	1.60 (0.76–3.33)	NS		
CEA ≤5.0 ng/ml				
Yes	1			
No	1.70 (0.88–3.31)	NS		
CA19-9 ≤37 IU/ml				
Yes	1			
No	1.19 (0.56–2.51)	NS		
Recurrent disease				
Yes	1			
No	1.30 (0.59–2.86)	NS		
Metastatic disease				
Yes	1			
No	0.71 (0.37–1.37)	NS		
Gallbladder carcinoma				
Yes	1			
No	1.62 (0.84–3.11)	NS		
Without ascites				
Yes	1		1	
No	2.77 (1.04–7.17)	0.033	3.21 (1.20–8.61)	0.020
Any response to first-line chemotherapy				
Yes	1		1	
No	2.10 (1.09–4.05)	0.023	2.29 (1.17–4.47)	0.015

CI, confidence interval; NS, not significant.

Table 3. Adverse events that occurred during S-1 monotherapy as the second-line treatment, according to CTCAE version 4.0

	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Anemia	23	17	1	0
Leucopenia	8	7	1	0
Neutropenia	8	5	1	0
Thrombocytopenia	15	4	1	0
Non-hematologic				
Anorexia	18	5	1	0
Nausea	6	7	1	0
Diarrhea	5	2	3	0
Mucositis oral	5	2	1	0
Fatigue	4	2	0	0
Dysgeusia	6	0	0	0
Skin hyperpigmentation	4	0	0	0
Vomit	2	1	0	0
Constipation	3	0	0	0
Rash	0	1	1	0
Watering eyes	2	0	0	0

Grade 3–4 adverse events were not frequent and no treatment-related death did occur.

Other treatment regimens were reported for the patients with BTC refractory to GEM (Table 4). Lee et al. (26) reported that the Conti-FAM regimen showed a response rate of 12% and an MST of 6.7 months with a TTP of 2.3 months. Pino et al. (27) reported that the CapCel regimen showed a response rate of 9% and an MST of 4.4 months with a PFS of 4.0 months. These studies suggest modest efficacy and safety; however, it is a problem that these studies included more patients with pancreatic cancer rather than with BTC. Recently, many molecular-targeting drugs are developed, and some of these are expected to be efficacious for advanced BTC. Paule et al. suggested the efficacy of the cetuximab plus GEM-oxaliplatin (GEMOX) regimen for patients who are refractory to GEMOX (28). The study enrolled a few patients and was limited to intrahepatic cholangiocarcinoma. However, cetuximab plus GEMOX was expected to be useful for the first-line treatment in the single-arm Phase II study (29), and cetuximab plus GEMOX will be one of the candidates for the standard care of second-line treatment after the GEM plus platinum. Lastly, sunitinib is also expected in the second-line treatment (30).

Brandi (31) analyzed EM plus platinum compound, capecitabine or irinotecan as a drug for second-line treatment for patients refractory to GEM in the first-line treatment. It asks the clinical questions whether or not GEM should be used in the second-line treatment for patients refractory to GEM in the first-line treatment. Indeed, 5-FU is the key drug in metastatic colorectal cancer, which should be used after failure to first-line regimen including itself (32,33). In advanced BTC, some clinical trials that investigate the usefulness of GEM-containing second-line treatment after the failure to GEM are ongoing in Japan, such as GEMOX (UMIN000003650) and fix-dose rate GEM plus S-1(UMIN000005918).

The efficacy of second-line chemotherapy by S-1 monotherapy and these reported regimens should be evaluated by placebo control studies because the result will change

Table 4. Other regimens reported about the second-line treatment of advanced biliary tract cancer

Author	Regimen	Patients (*n*)	GBC	Response rate (%)	Median TTP or PFS (months)	Median survival time (months)
Lee et al.	Conti-FAM	16	31.3%	12	2.3	6.7
Pino et al.	CapCel	35	14%	9	4.0	4.4
Paule et al.	GEMOX + Cet	9	0	22	4.0	7.0
Yi et al.	Sunitinib	56	26.8%	8.9	1.7	4.8
Brandi et al.	GEM + platinum or GEM + capecitabine or GEM + CPT-11	49	12.2%	—	3.5	8.1

Conti-FAM; continuous 5-fluorouracil, doxorubicin and mitomycin-C; CapCel, capecitabine and celecoxib; GEMOX, gemcitabine and oxaliplatin; Cet, cetuximab; GEM, gemcitabine; CPT-11, irinotecan; GBC, gallbladder carcinoma; TTP, time to progression PFS; progression free survival.

because of the patient's background. Nevertheless, it is difficult to carry out a randomly controlled study, which compares S-1 monotherapy with placebo, since S-1 is approved for advanced biliary tract cancer by social insurance in Japan. Therefore, S-1 monotherapy can be the control arm in the clinical trials that test new promising regimens in the future.

In conclusion, S-1 monotherapy in a practical setting is well tolerated, and its efficacy is almost the same as the prospective clinical trials for patients with advanced BTC refractory to a GEM-containing regimen. Further development and randomized controlled studies of the second-line treatment are warranted.

Conflict of interest statement

None declared.

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Cetuximab

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索引用語：EGFR，cetuximab，胆道癌，膵癌

1 はじめに

Cetuximab（商品名：アービタックス）は，ヒト上皮細胞増殖因子受容体（EGFR）を標的とする免疫グロブリンG（IgG1）サブクラスのキメラ型ヒト/マウスモノクローナル抗体であり，生物応答調節薬である．大腸癌，頭頸部癌を対象にした臨床試験で有効性が証明され，本邦でも2008年7月に「EGFR陽性の治癒切除不能な進行・再発結腸・直腸癌」に対して承認を受け，頭頸部癌に対しても承認申請が行われている薬剤である．一方，cetuximabは，膵臓癌，胆道癌に対しても臨床試験が行われ，その有効性が探索されてきた．

本稿では，EGFRのシグナル伝達経路について概説したのち，膵臓癌ならびに膵臓癌に対するcetuximabの現在までに明らかとなっている臨床成績と今後の方向性について述べる．

2 癌におけるEGFR経路

EGFR（HER1, ErbB1）は，上皮系細胞などに存在する細胞膜貫通型受容体のひとつである．EGFRに結合する細胞増殖因子（リガンド）には，EGF，トランスフォーミング増殖因子（transforming growth factor; TGF）-α，amphiregulin，betacellulin，ヘパリン結合性EGF様増殖因子（HB-EGF），epiregulinなどがある．EGFR細胞外ドメインへのリガンド結合によって，EGFRは三次元構造が変化し，EGFRもしくは他のHERファミリー分子（HER2, HER3, HER4）と二量体を形成し，細胞内チロシンキナーゼの活性化，隣接した互いのチロシン残基の活性化（自己リン酸化）が生じ，さらに下流へと情報伝達が生じる．EGFR下流の経路には，RAS/RAF/MEK/ERK経路やPI3K/AKT経路，JAK/STAT経路などが知られている（図1）．

EGFR経路のシグナル伝達は，正常細胞では細胞の分化，増殖，発達，維持の調節に重要な役割を果たしている[1,2]．一方で，癌組織ではしばしばEGFRの機能が異常に亢進しており，癌の増殖，浸潤，転移，生存，血管新生などに関与している．

Hiroya TANIGUCHI et al: Cetuximab
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