果は，主要評価項目である全生存において，ベバシズマブの上乗せが認められないという残念な結果となりました[7]．また，その治療成績に「地域間差」があることが浮き彫りとなりました．

Q グローバルトライアルにおける「地域間差」とはなんですか？

A 我が国で行われたSPIRITS試験とグローバル試験として行われたFLAGS trialを比較してみましょう．すると，二次治療の地域間差について興味深い点が浮かび上がってきます．それは両者の二次治療への移行率の差が顕著なことです．SPIRITS試験の二次治療への移行率は75％と高率なのに対し，グローバルトライアルであるFLAGS trialでは，わずか31％の移行率にしかすぎません．この移行率の低さは，近年報告された他の試験においても共通して認められています．

ToGA試験においても，アジアにおけるトラスツズマブの生存に対するインパクトは小さく，南米における生存に対するインパクトは極めて大きなものがありました．この理由を考えてみると，前述した二次治療の地域間差が第一に考えられます．この試験の登録の半分近くは，韓国ならびに我が国から行われています．日韓は，実臨床において二次治療を積極的に行っている地域ですが，南米では二次治療が行われることは少ない地域です．よって南米では，一次治療のインパクト，すなわちトラスツズマブのインパクトが大きくなったと考えられます．現在胃がんにおける分子標的治療薬の開発は，日韓がメインとなっていますが，多くの患者が日韓から登録された場合，二次治療以降の生存が長いことから，主要評価項目が全生存期間だと有意な差がつきにくいという新たな問題が生まれています．これからは，従来どおりのグローバルトライアルを積極的に展開すべきなのか，practice cultureが同じ地域でのトライアルを計画すべきなのか慎重に考えないといけないと思われます．

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Ⅳ．進行・再発大腸癌に対する標準的化学療法

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大腸癌領域に分子標的治療薬が導入されてある程度の時間が経過し，各薬剤の特性が明らかとなってきた。今後しばらくは新薬の導入予定がなく，現在使用可能な薬剤を患者の病態に応じていかに提供するのがベストかを問う時代になってきたと思われる。わが国の大腸癌治療ガイドラインも2010年7月に改訂され，first-lineの選択肢はNCCNのpractice guidelineとほぼ同様となった。これら多くの治療選択肢は実臨床における標準的治療として位置付けられるものであり，正に患者個々の病態に応じた選択が可能であることを意味している。

1．First-line治療をどのように選択するのか

患者の治療目標は，患者個々によって違いがあって当然である。その治療目標によってaggressive approachが必要か，あるいはnon-aggressive approachが必要かを見極める必要がある。図1に最近欧米で考えられているfirst-lineの治療戦略を示す。first-line治療においてaggressive approachが必要か否かを見極める上で，第一に治癒切除の可能性がないかどうかを検討することが重要である。治癒切除が可能な症例では，当然腫瘍縮小効果の高いaggressive approachを選択すべきである。次に，治癒切除が不可能と考えられる症例においてもaggressive approachが必要なケースがある。それは腫瘍随伴症状のある症例である。さらに腫瘍随伴症状がない症例においても，腫瘍量の多い症例や急激な臨床経過をたどることが予想される症例ではaggressive approachが必要となろう。それ以外の症例はnon-aggressive approachで十分対応可能である。

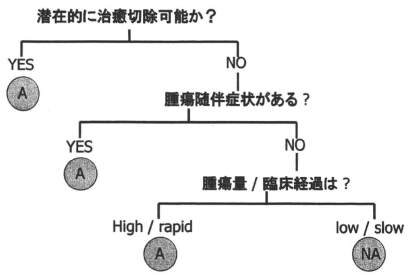

図1　First-line治療の選択
A: aggressive approach, NA: non-aggressive approach

2．Aggressive approachの選択

前述したようにaggressive approachが必要な症例は，いい換えれば急速な腫瘍縮小が不可欠の症例である。その場合のbaseline regimenとなるのはFOLFOXあるいはFOLFIRIである。それらbaseline regimenにどの分子標的治療薬を併用すべきか議論のあるところである。抗EGFR抗体薬のcetuximabやpanitumumabは，*K-RAS* wild typeの場合に限りその効果が期待できる。これまでに行われたfirst-lineの検証試験の結果から，*K-RAS* wild typeの症例においては，抗EGFR抗体薬の方がbaseline regimenに対する奏効率の上乗せが期待できる（表1）。よって*K-RAS* wild typeの症例でaggressive approachが必要な症例は，抗EGFR抗体薬の選択がreasonableな選択だと思われる[1-3]。

その一方で，抗VEGF抗体薬のbevacizumabは，*K-RAS* statusに関係なく効果が期待できる。*K-RAS* mutantでaggressive approachが必要な症例は，治癒切除を目標にする症例か否かでその選択が違ってくるかもしれない。つまり最終的に治癒切除を目標とした症例においては，bevacizumabをbaseline regimenと併用するか否かで現状意見が分かれているからである。その根拠として，bevacizumabの検証試験であるNO16966試験の奏効率において，bevacizumabの上乗せがまったく認められなかった点があげられる[1]。この試験結果と手術時期を遅らせる必要性から，たとえ*K-RAS* mutantの症例であったとしてもconversion therapyにおいてbeva-

表1　一次療法における各抗体薬併用による奏効率の上乗せ

	baseline regimen	control群	抗体薬併用群
NO16966試験（bevacizumab）	FOLFOX	36%	38%
	XELOX	39%	37%
CRYSTAL試験（cetuximab）	FOLFIRI	40%	57%
PRIME試験（panitumumab）	FOLFOX	48%	55%

cizumab は必要ないと考える欧米の研究者も多い。逆に *K-RAS* mutant において，治癒切除を目標としない aggressive approach が必要な症例の場合は，bevacizumab 併用を否定する理由は見当たらず，baseline regimen への bevacizumab の併用がベターな選択と考えられる。

3．Non-aggressive approach の選択

non-aggressive approach で対応可能な症例としては，治癒切除が望めず腫瘍量のそれほど多くない，腫瘍増殖スピードの slow な症例があげられる。そういった症例の治療目標は，QOL を維持した状態での生存期間の延長であり，できる限り低い毒性での延命が求められる。実際に有効性を落とさずに毒性を抑える試みとして OPTIMOX 試験がある[4,5]。日常臨床で使用される頻度の多い FOLFOX の最大の問題点である神経毒性を軽減するために Oxaliplatin を 6 コース限定で使用し，そのあと 5-FU/LV による維持療法を行い，可能であれば FOLFOX を再導入するといった戦略である。この OPTIMOX コンセプトによって腫瘍をコントロールする期間を減弱することなく，Oxaliplatin による grade 3 以上の神経毒性が軽減され，患者の QOL 向上につながった。

同じく QOL 維持における分子標的治療薬の役割を考える上で重要な発表が 2010 年 ASCO で報告されている。これはスペインの TTD グループが報告した MACRO 試験で，XELOX＋bevacizumab を PD まで続ける群をコントロールにして，XELOX＋bevacizumab を 6 コース行い，その後に維持療法として bevacizumab 単独を投与する群の非劣性を検討した試験である[6]。残念ながら統計学的には，bevacizumab 単独群の非劣性は証明されなかったが，QOL を強く意識した極めてチャレンジングな興味深い試験であった。今後わが国においても，患者の QOL 向上をめざした臨床試験を考えていく必要があると思われる。

いくつかの臨床試験の結果から，bevacizumab の上乗せ効果を無増悪生存期間におけるハザード比でみた場合，5-FU/LV（RPMI）＞IFL＞capecitabine＞XELOX＞FOLFOX の順となる。単純に考えると，5-FU/LV との併用で最大の効果が得られ（ハザード比 0.49），逆に実臨床で頻用されることの多い FOLFOX において上乗せ効果が最も弱い（ハザード比 0.89）。もちろん毒性の点からいえば 5-FU/LV＋bevacizumab は less toxic regimen であり，sequential approach で残りの key drugs を使い切ることが可能であれば，baseline regimen を必ずしも combination regimen にする必要はないと思われる。以前，細胞毒性を有する抗癌剤の使用に際し，毒性軽減を考えて sequence と combination の比較が検討され，両者には大差がないことが報告されている[7,8]。そこにさらに分子標的治療薬が加わった今，毒性軽減を目指した sequential approach が同様に成り立つのか興味深いところである。極論すれば，腫瘍量の少ない無症状の患者においては，そういった sequence の戦略が一番フィットするのではないかと考える。

おわりに

分子標的治療薬の登場によって飛躍的に治療選択肢が増え，種々のガイドラインに記載されているように，様々な治療のオプション選択が可能となった。実際の臨床においては，決して画一的な治療選択をすべきではなく，病態に応じた治療選択が重要な時代になりつつある。それを実践していくには，まず一次治療開始前に aggressive approach が必要な症例かどうかを見極めることが重要である。

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Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan

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Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan

T Okusaka*[,1], K Nakachi[2], A Fukutomi[3], N Mizuno[4], S Ohkawa[5], A Funakoshi[6], M Nagino[7], S Kondo[8], S Nagaoka[9], J Funai[9], M Koshiji[9], Y Nambu[9], J Furuse[10], M Miyazaki[11] and Y Nimura[12]

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BACKGROUND: A British randomised study of gemcitabine plus cisplatin (GC) combination showed promising results in biliary tract cancer (BTC) patients. In our study, we evaluated the efficacy and safety of this combination compared with gemcitabine alone (G) in Japanese BTC patients.

METHODS: Overall, 84 advanced BTC patients were randomised to either cisplatin 25 mg m^{-2} plus gemcitabine 1000 mg m^{-2} on days 1, 8 of a 21-day cycle (GC-arm), or single-agent gemcitabine 1000 mg m^{-2} on days 1, 8 and 15 of a 28-day cycle (G-arm). Treatments were repeated for at least 12 weeks until disease progression or unacceptable toxicity occurred, up to a maximum of 48 weeks.

RESULTS: A total of 83 patients were included in the analysis. For the GC and G-arms, respectively, the 1-year survival rate was 39.0 *vs* 31.0%, median survival time 11.2 *vs* 7.7 months, median progression-free survival time 5.8 *vs* 3.7 months and overall response rate 19.5 *vs* 11.9%. The most common grade 3 or 4 toxicities (GC-arm/G-arm) were neutropenia (56.1%/38.1%), thrombocytopenia (39.0%/7.1%), leukopenia (29.3%/19.0%), haemoglobin decrease (36.6%/16.7%) and γ-GTP increase (29.3%/35.7%).

CONCLUSIONS: Gemcitabine plus cisplatin combination therapy was found to be effective and well tolerated, suggesting that it could also be a standard regimen for Japanese patients.

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Keywords: combination chemotherapy; gemcitabine; cisplatin; biliary tract cancer

Although biliary tract cancer (BTC) is a rare type of cancer throughout the world, it is more prevalent in East Asia and Latin America than in other countries (Matsuda and Marugame, 2007; Randi *et al*, 2009). According to 'Demographic Statistics in Japan (2009)' (compiled by the Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare (MHLW)), the number of deaths due to BTC was 17 311 in 2007, making this cancer the sixth leading cause of cancer death in Japan.

Despite great progress in diagnostic imaging, most cases of BTC are diagnosed as advanced and inoperable. Even if the tumour is not locally advanced, the primary tumour site is often contiguous with vital organs such as the liver, pancreas, or duodenum, or with major vessels such as the portal vein or hepatic artery. This anatomical peculiarity precludes resection of tumours in many cases. Furthermore, even if curative-intent surgical resection is performed, the cancer often relapses due to its invasive nature and its anatomical characteristics.

Systemic chemotherapy is usually indicated for patients with unresectable, advanced BTC or for those who have relapsed after operation; however, no standard treatment has yet been established for such patients. Gemcitabine hydrochloride is a deoxycytidine derivative that inhibits DNA elongation through intracellular phosphorylation of ribonucleotide reductase. In Japan, a single-arm Phase II study in patients with unresectable BTC confirmed that gemcitabine monotherapy had moderate efficacy and manageable toxicity, both of which were comparable with approved treatments for other cancers (Okusaka *et al*, 2006).

As gemcitabine had also been found to exhibit synergistic effects on cytotoxic activity *in vitro* and *in vivo* when combined with cisplatin (Peters *et al*, 1995; Bergman *et al*, 1996), clinical studies were conducted in various cancers with this combination. Results from these studies eventually led to use of the gemcitabine plus cisplatin (GC) combination as one of the standard treatments for non-small cell lung cancer and bladder cancer.

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The combination of GC has also been studied by many researchers for the treatment of BTC (Park *et al*, 2006; Eckel and Schmid, 2007; Pasetto *et al*, 2007; Lee *et al*, 2008). So far, the largest randomised Phase III study has been the recent UK ABC-02 study, in which the efficacy and safety of gemcitabine 1000 mg m^{-2} alone *vs* the combination of gemcitabine 1000 mg m^{-2} plus cisplatin 25 mg m^{-2} was evaluated by British research groups (Cancer Research UK and University College London). That study was initiated as a randomised phase II study with gemcitabine alone *vs* GC (UK ABC-01 study) and then was expanded to a phase III study (ABC-02 study) (Valle *et al*, 2009a, b).

Our study was planned to follow-up on an earlier study of gemcitabine monotherapy conducted in Japanese BTC patients (Okusaka *et al*, 2006). Given the encouraging results from the UK ABC-01 study, we conducted this study to (1) evaluate both gemcitabine monotherapy and the GC combination in Japanese BTC patients, and (2) determine whether benefits similar to those observed in the UK study could be obtained for the combination regimen.

The primary objective of the study was to compare the 1-year survival rate in patients with BTC who received one of these two therapies. The secondary objectives included response rate, progression-free survival (PFS) and assessment of safety.

MATERIALS AND METHODS

Study design

This was a multicentre, randomised phase II study to evaluate the efficacy and safety of GC combination compared with single-agent gemcitabine in chemotherapy-naive patients with locally advanced or metastatic BTC. Patients were randomised to either single-agent gemcitabine 1000 mg m^{-2} on days 1, 8 and 15 of a 28-day cycle (G-arm) or cisplatin 25 mg m^{-2} followed by gemcitabine 1000 mg m^{-2} on days 1, 8 of a 21-day cycle (GC-arm). Randomisation was stratified by primary site (gallbladder cancer or other BTC) and the presence or absence of primary tumour.

Eligibility criteria

Eligible patients met the following criteria: histologically confirmed unresectable locally advanced or metastatic cancer of the biliary tract; no history of earlier chemotherapy; performance status of 0 or 1; a life expectancy of at least 3 months; at least 20 years of age at the time of study entry; adequate function of major organs (haemoglobin $\geqslant$10 g per 100 ml, white blood cells $\geqslant$3000/mm^3, neutrophils $\geqslant$1500/mm^3, platelets $\geqslant$100 000/mm3, AST/ALT/ALP $\leqslant$3 times upper limit of normal (ULN), total bilirubin $\leqslant$2 times ULN, $\leqslant$3 times ULN for patients with obstructive jaundice or metastases to the liver, serum creatinine $\leqslant$1.5 times ULN, creatinine clearance or 24-h creatinine clearance $\geqslant$45 ml min^{-1}).

This study followed the ethical principles that have their origins in the Declaration of Helsinki, and was conducted in accordance with the protocol, the 'ordinance on Good Clinical Practice' and related regulations. Written informed consent was obtained from all patients who were considered eligible for participation in this study before enrolment. The Efficacy and Safety Evaluation Committee, an independent review board, was consulted if any efficacy and safety issues arose in the study.

Study treatment

The assigned treatment was given for a minimum of 12 weeks (at least four cycles in the GC-arm and three cycles in the G-arm) and continued to a maximum of 48 weeks (up to 16 cycles in the GC-arm and up to 12 cycles in the G-arm), unless disease progression (PD) was evident, an intolerable adverse event occurred or the patient was required to withdraw from the study.

Efficacy and safety assessment

All patients who received at least 1 dose of the study drug were included in the efficacy and safety assessment. Response rate was evaluated according to the Response Evaluation Criteria in Solid Tumors. Evaluation of tumours after patient randomisation was performed every 6 weeks until PD. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0).

Statistical design and analysis

The sample size was calculated by the selection method of Simon (Simon *et al*, 1985), which is based on the proposition that GC combination therapy is selected if the 1-year survival rate for the GC-arm is higher than that for the gemcitabine arm. We assumed a 1-year survival rate of 25% for the G-arm and 35% for GC-arm (Okusaka *et al*, 2006; Park *et al*, 2006). With these assumptions, 30 patients per arm were needed to appropriately select the combination therapy with a probability of $\geqslant$80%. To optimise safety and efficacy information, the sample size was set to 42 patients per arm.

The Kaplan–Meier method was used to estimate 1-year survival (primary outcome), PFS and 6-month PFS rates (secondary outcomes) for each treatment arm; 95% confidence intervals (CIs) were calculated. A Cox proportional hazards model was used to calculate the hazard ratio, 95% CI and its two-tailed *P*-value. Fisher's exact test was used to compare the patient characteristics, response and disease control rates, and toxicities between the two treatment arms. The exact CIs were calculated based on binomial distributions.

RESULTS

Patients

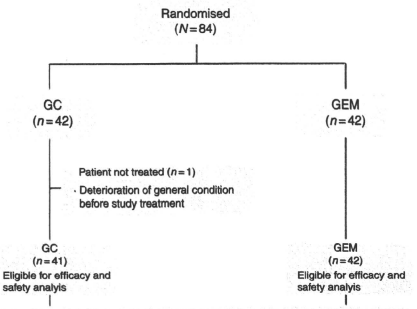
This study was carried out from September 2006 to October 2008 at nine study centres in Japan. Eighty-four patients were randomised to either gemcitabine monotherapy (G-arm) or GC combination (GC-arm). One patient assigned to the GC-arm was not treated because the general condition of the patient deteriorated before study treatment. All of the remaining 83 patients, 41 in the GC-arm and 42 in the G-arm, received at least 1 dose of study treatment. Efficacy and safety were evaluated for each of these 83 patients (Figure 1). Demographic variables (Table 1) were well balanced between the two treatment arms, except for patients with ampullary carcinoma (4 in GC-arm, 0 in G-arm).

Drug exposure and duration of the treatments

A total of 247 (median 6.0) and 203 (median 4.0) cycles were administered in the GC-arm and G-arm, respectively. Relative dose intensities were 78.9% for gemcitabine and 79.0% for cisplatin in the GC-arm, and 87.4% for gemcitabine in the G-arm. Three patients in the GC-arm and two patients in the G-arm completed 48 weeks treatment.

Efficacy

A total of 83 patients were evaluable for tumour response according to the protocol, 41 in the GC-arm and 42 in the G-arm. No complete tumour responses were observed. In total, eight patients in the GC-arm had a partial response (PR) compared with five patients in the G-arm (PR 19.5 *vs* 11.9%). In addition,



Reasons for discontinuation	GC arm	GEM arm
Progression of disease	25	34
Unable to start next cycle	4	0
Adverse event	7	3
Patient decision	1	3
Physician decision	1	0
Completed study (48 weeks)	3	2

Figure 1 CONSORT diagram. Disposition of patients. GC = gemcitabine–cisplatin combination; GEM = gemcitabine alone.

20 patients had stable disease in the GC-arm *vs* 16 patients in the G-arm (SD 48.8 *vs* 38.1%). The disease control rate (CR + PR + SD) was 68.3% (95% CI: 51.9, 81.9) *vs* 50.0% (95% CI: 34.2, 65.8) in favour of the combination therapy. The 1-year survival rate (39.0 *vs* 31.0%), median survival time (11.2 months *vs* 7.7 months) and median PFS (5.8 months *vs* 3.7 months) were better for the GC-arm *vs* G-arm (Figure 2). The hazard ratio between the GC and G-arms was 0.69 (95% CI: 0.42, 1.13) for overall survival (OS) and 0.66 (95% CI: 0.41, 1.05) for PFS (Table 2).

As shown in Table 3, the prognosis for patients with gallbladder cancer was worse than that for patients with non-gallbladder cancer; however, the median survival times were longer with the GC combination in gallbladder cancer patients (9.1 months *vs* 6.7 months), as well as in patients with non-gallbladder cancer (13.0 months *vs* 8.0 months). The prognosis for patients with primary tumours was worse than that for patients without primary tumours; however, the GC therapy showed longer median survival time in both patient subgroups (9.4 months *vs* 7.4 months in the patients with primary tumours, 16.1 months *vs* 12.7 months in the patients without primary tumours).

Safety

All adverse events observed in this study were predictable and manageable based on the safety profile of GC. As shown in Table 4, the most common grade 3 or higher adverse events (⩾25%) were neutropenia (56.1%), thrombocytopenia (39.0%), haemoglobin decrease (36.6%), RBC decrease (34.1%), leukopenia (29.3%) and γ-GTP increase (29.3%) in the GC-arm, and neutropenia (38.1%) and γ-GTP increase (35.7%) in the G-arm. The incidence of haematotoxicity was higher in the GC-arm; grade 3 or more serious C-reactive protein increase was detected only in the monotherapy arm.

Table 1 Patient characteristics

Characteristic	GC (*N* = 41) *n* (%)	GEM (*N* = 42) *n* (%)	*P*-value
Gender			
Male	18 (43.9)	21 (50.0)	0.662
Female	23 (56.1)	21 (50.0)	
Age (year)			
Median	65.0	66.5	0.0812[a]
Range	43–80	49–78	
PS			
0	34 (82.9)	28 (66.7)	0.129
1	7 (17.1)	14 (33.3)	
Primary tumour sites			
Extrahepatic bile duct	8 (19.5)	11 (26.2)	0.239
Intrahepatic bile duct	14 (34.1)	14 (33.3)	
Gallbladder	15 (36.6)	17 (40.5)	
Ampulla	4 (9.8)	0 (0.0)	
Metastatic sites			
Liver	22 (53.7)	20 (47.6)	0.663
Regional lymph nodes	23 (56.1)	28 (66.7)	0.372
Distant lymph nodes	19 (46.3)	18 (42.9)	0.827
Lung	8 (19.5)	7 (16.7)	0.782
Peritoneum	7 (17.1)	7 (16.7)	1.000
Bone	0 (0.0)	1 (2.4)	1.000
Others	3 (7.3)	3 (7.1)	1.000
Initial onset or recurrence			
Initial onset	30 (73.2)	32 (76.2)	0.804
Recurrence after surgery	11 (26.8)	10 (23.8)	
Histological type			
Adenocarcinoma	39 (95.1)	41 (97.6)	0.616
Adenosquamous cancer	2 (4.9)	1 (2.4)	
Disease stage (gallbladder cancer, extrahepatic bile duct cancer, ampulla cancer)			
IIA	0 (0.0)	0 (0.0)	1.000
IIB	3 (7.3)[b]	2 (4.8)[b]	
III	2 (4.9)	2 (4.8)	
IV	16 (39.0)	17 (40.5)	
Recurrence after surgery	6 (14.6)	7 (16.7)	
Disease stage (intrahepatic bile duct cancer)			
II	0 (0.0)	1 (2.4)[b]	0.389
IIIA	0 (0.0)	1 (2.4)	
IIIB	0 (0.0)	0 (0.0)	
IIIC	0 (0.0)	2 (4.8)	
IV	9 (22.0)	7 (16.7)	
Recurrence after surgery	5 (12.2)	3 (7.1)	
Biliary drainage			
No	25 (61.0)	24 (57.1)	0.824
Yes	16 (39.0)	18 (42.9)	
Previous therapy			
No	30 (73.2)	28 (66.7)	0.855
Surgery	11 (26.8)	12 (28.6)	
Radiotherapy	0 (0.0)	1 (2.4)	
Surgery and radiotherapy	0 (0.0)	1 (2.4)	

Abbreviations: GC = gemcitabine and cisplatin; GEM = gemcitabine; PS = performance status. [a]*t*-test. [b]Patients were diagnosed as having unresectable disease with marked regional node metastases involving the proper hepatic artery and/or main portal vein.

There were no treatment related deaths. Most of the patients recovered from the above adverse events by reducing or discontinuing the study treatment.

Post-study chemotherapy

Thirty patients in the GC-arm received post-study chemotherapy including S-1, tegaful/gimeracil/oteracil potassium (19 patients), gemcitabine (10 patients) and tegaful/uracil (1 patient). In the G-arm, 33 patients received post-study chemotherapy including S-1 (20 patients), gemcitabine (11 patients), cisplatin/fluorouracil (1 patient) and doxorubicin/tegaful/uracil (1 patient).

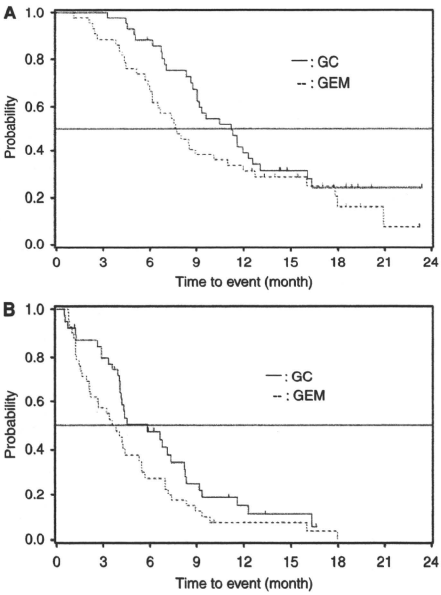


Figure 2 Kaplan–Meier curve of overall survival and progression-free survival. (**A**) Overall survival. (**B**) Progression-free survival. GC = gemcitabine–cisplatin combination; GEM = gemcitabine alone; CI = confidence interval.

DISCUSSION

Although this study (BT22 study) showed that gemcitabine monotherapy and the GC combination were both active in Japanese patients with advanced BTC, a superior benefit was obtained with the combination treatment. In the GC/G-arms, the 1-year survival rate was 39.0%/31.0%, median survival time was 11.2/7.7 months and median PFS time was 5.8/3.7 months (Table 2).

The UK ABC-02 study, which was conducted with the same dose and regimen as this study (Valle *et al*, 2009b), showed a similar benefit for the GC combination. The respective median survival/PFS times in that study were 11.7/8.5 months in their GC-arm, and 8.2/6.5 months in their G-arm.

The hazard ratios reported in the ABC-02 study for OS (0.68, 95% CI: 0.53, 0.86) and PFS (0.70, 95% CI: 0.56, 0.88) compared well with the respective values from our study: 0.69 (95% CI: 0.42, 1.13) and 0.66 (95% CI: 0.41, 1.05). As the number of patients was based on Simon's selection method (Simon *et al*, 1985), this study was not designed to compare and identify statistical significant differences between the two treatment arms. These hazard ratios

Table 3 Overall survival time by stratification factor

Median survival time (months) (95% CI)	GC (*N* = 41)	GEM (*N* = 42)	*P*-value
Tumour site			
Gallbladder	9.1 (6.9, 11.6)	6.7 (4.2, 11.0)	0.675
Non-gallbladder	13.0 (9.2, ***)	8.0 (6.1, 16.0)	0.110
Primary tumour			
Presence of primary tumour	9.4 (8.7, 11.6)	7.4 (5.9, 8.5)	0.253
Absence of primary tumour	16.1 (12.3, ***)	12.7 (6.5, ***)	0.389

Abbreviations: GC = gemcitabine and cisplatin; GEM = gemcitabine; CI = confidence interval. ***denotes upper limits are not available.

Table 2 Summary of time-to-event end points: overall response and survival

	GC (*N* = 41) *n* (%)	GEM (*N* = 42) *n* (%)	*P*-value
Overall response rate			
Complete response (CR)	0 (0.0)	0 (0.0)	
Partial response (PR)	8 (19.5)	5 (11.9)	
Stable disease (SD)	20 (48.8)	16 (38.1)	
Progressive disease (PD)	9 (22.0)	17 (40.5)	
Not evaluable (NE)	4 (9.8)	4 (9.5)	
Response rate (95% CI)	19.5% (8.8, 34.9)	11.9% (4.0, 25.6)	0.380
Disease control rate (CR+PR+SD) (95% CI)	68.3% (51.9, 81.9)	50.0% (34.2, 65.8)	0.119
Overall survival			
1-year survival rate (95% CI)	39.0% (23.7, 54.4)	31.0% (17.0, 44.9)	
Median survival time (95% CI)	11.2 months (9.1, 12.5)	7.7 months (6.1, 11.0)	
Hazard ratio (95% CI)	0.69 (95% CI: 0.42, 1.13)		0.139
Progression-free survival (PFS)			
Median PFS (95% CI)	5.8 months (4.1, 8.2)	3.7 months (2.1, 5.3)	
Hazard ratio (95% CI)	0.66 (95%CI: 0.41, 1.05)		0.077
6-Months PFS rate (95% CI)	47.4% (31.4, 63.4)	27.7% (14.0, 41.5)	

Abbreviations: GC = gemcitabine and cisplatin; GEM = gemcitabine; CI = confidence interval.

Table 4 Summary of maximum toxicity grades[a] (incidence ⩾30%)

	GC ($N=41$)			GEM ($N=42$)			
	Maximum toxicity grade			Maximum toxicity grade			
Events	**Grade 3 (%)**	**Grade 4 (%)**	**All grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All grades (%)**	***P*-value**
Haematological							
WBC count decreased	29.3	0	87.8	19.0	0	69.0	0.061
Haemoglobin decreased	26.8	9.8	85.4	9.5	7.1	85.7	1.000
Neutrophil count decreased	39.0	17.1	82.9	28.6	9.5	69.0	0.200
Platelet count decreased	26.8	12.2	80.5	4.8	2.4	76.2	0.791
RBC decreased	34.1	0	75.6	14.3	0	78.6	0.798
Haematocrit decreased	4.9	0	58.5	0	0	54.8	0.826
Non-haematological							
Anorexia	0	0	80.5	4.8	0	61.9	0.090
Nausea	0	0	68.3	0	0	42.9	0.027
Fatigue	0	0	58.5	2.4	0	50.0	0.511
AST increased	17.1	0	53.7	14.3	2.4	52.4	1.000
ALT increased	24.4	0	51.2	16.7	0	52.4	1.000
Vomiting	0	0	48.8	0	0	23.8	0.023
GGT increased	29.3	0	46.3	31.0	4.8	50.0	0.827
Pyrexia	0	0	43.9	4.8	0	57.1	0.190
LDH increased	0	0	36.6	0	0	35.7	1.000
Constipation	0	0	36.6	0	0	33.3	0.820
ALP increased	7.3	0	31.7	16.7	0	40.5	0.495
Weight decreased	0	0	31.7	0	0	31.0	1.000
Diarrhoea	2.4	0	31.7	0	0	26.2	0.634
Blood sodium decreased	17.1	0	31.7	9.5	0	19.0	0.214
C-reactive protein increased	0	0	26.8	7.1	0	52.4	0.025

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GC = gemcitabine and cisplatin; GEM = gemcitabine; GGT = γ-glutamyltransferase; LDH = lactate dehydrogenase; RBC = red blood cell; WBC = white blood cell. [a]Events were graded according to CTCAE v3.0.

strongly suggest that the GC combination has superior benefit compared with single-agent gemcitabine, even though there were no statistical significant differences in survival and PFS between the two arms in our study.

Although there have been many single-arm Phase II studies of the GC combination for BTC (Thongprasert *et al*, 2005; Kim *et al*, 2006; Charoentum *et al*, 2007; Meyerhardt *et al*, 2008; Valle *et al*, 2009a), these results have never been distilled to one fixed dose and regimen of GC. Many previous studies of GC combination reported relatively higher response rates, but with more serious treatment-related adverse events (Thongprasert *et al*, 2005; Kim *et al*, 2006; Charoentum *et al*, 2007; Meyerhardt *et al*, 2008). In the phase II study conducted by Thongprasert *et al* (2005), 17.85% of the patients who were treated with the GC combination required dose reduction, and in another Phase II study recently conducted by Meyerhardt *et al* (2008), dose reductions and study withdrawals were required for 50% of the patients who received the combination therapy. In our study, we also observed more frequent adverse events with the doublet (Table 4). However, as shown in Figure 1, only seven patients (17%) discontinued from the study because of adverse events and four patients (9.7%) required dose adjustments in the GC-arm.

Overall, the toxicity observed in this study was manageable. Although interstitial pneumonia was detected in one patient from each of the arms, both patients recovered with appropriate treatment. One grade 3 renal failure and one grade 2 peripheral neuropathy were observed in GC-arm, in line with similar events seen in previous studies of the GC combination (Thongprasert *et al*, 2005; Kim *et al*, 2006; Charoentum *et al*, 2007; Meyerhardt *et al*, 2008; Valle *et al*, 2009a). It is to be noted that despite the higher incidence of haematotoxicity in patients receiving the combination therapy, drug-caused myelosuppression did not result in febrile neutropenia or bleeding. Grade 3 or greater increases in C-reactive protein were observed only in the gemcitabine monotherapy-arm, also suggesting that the combination therapy did not increase neutropenic infections.

In this study, we stratified patients into those with gallbladder cancer and those with other BTCs. Gallbladder cancer has been reported to have a different biological behaviour (Kim *et al*, 2006; Doval *et al*, 2004; Jarnagin *et al*, 2006); furthermore, a pooled analysis by Eckel and Schmid (2007) revealed a higher response rate to chemotherapy and shorter OS for gallbladder cancer compared with other BTCs. As shown in Table 3, patients with gallbladder cancer showed worse survival than patients with other BTCs, this being consistent with previous reports (Eckel and Schmid, 2007; Wagner *et al*, 2009). It is important to note that median survival times were longer with the GC combination in patients with gallbladder cancer (9.1 months *vs* 6.7 months), as well as in patients with non-gallbladder cancer (13.0 months *vs* 8.0 months), suggesting that the combination therapy has greater benefit than monotherapy in gallbladder cancer and other BTC patients.

Another stratification factor used for this study was the presence or absence of a primary tumour, not a commonly used stratification factor in clinical trials for advanced BTC. Locally advanced or metastatic cancer, the stratification factor used in the UK ABC-01 and UK ABC-02 studies, is more commonly used, as both of these have been shown to affect OS in advanced BTC (Park *et al*, 2009). However, considering the importance of surgical resection of the primary tumour, we decided to use this as a stratification factor for patients in this study. As shown in Table 3, patients with primary tumours showed remarkably worse survival than patients without primary tumours. However, because of the limited number of patients in our subanalyses, the results should be viewed with caution, and the usefulness of this prognostic factor should be evaluated in future studies. We will continue our efforts

in collaboration with the UK ABC-02 study group to identify prognostic factors in a larger population, which may significantly affect clinical studies in BTC.

Despite the heterogeneous nature of BTC and the ethnic differences reported for this tumour type (Goodman and Yamamoto, 2007; Aljiffry *et al*, 2009), the outcomes from this study showed striking similarity with the large-scale phase III study (UK ABC-02) results. This suggests that cisplatin 25 mg m^{-2} plus gemcitabine 1000 mg m^{-2} on days 1 and 8 of a 21-day cycle would be beneficial in the treatment of advanced BTC.

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Conflict of interest

TO, KN, NM, SO, SK and JF have received honoraria, and YN, MK, JF and SN are employed by Eli Lilly Japan.

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original article

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Phase II study of S-1 plus leucovorin in patients with metastatic colorectal cancer

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Background: S-1, a novel oral fluoropyrimidine, is well tolerated in patients with metastatic colorectal cancer (mCRC). The response rate of S-1 for colorectal cancer is high, ranging from 35% to 40%. This study aimed to evaluate the safety and efficacy of S-1 combined with oral leucovorin (LV) to enhance antitumor activity in chemotherapy-naive patients with mCRC.

Patients and methods: S-1 was given orally twice daily for two consecutive weeks at a daily dose of 80–120 mg, followed by a 2-week rest period, within a 4-week cycle. LV was given orally twice a day at a daily dose of 50 mg, simultaneously with S-1.

Results: Of the 56 patients with previously untreated mCRC, 32 (57%) had partial responses. The median follow-up period was 27.2 months. The median time to progression was 6.7 months (95% confidence interval 5.4–7.9). The median survival time was 24.3 months. There was no treatment-related death or grade 4 toxicity. The most common grade 3 toxic effects were diarrhea (32%), anorexia (21%), stomatitis (20%), and neutropenia (14%).

Conclusion: S-1 combined with LV therapy demonstrated promising efficacy and acceptable safety in chemotherapy-naive patients with mCRC without the concurrent use of irinotecan, oxaliplatin, or molecular-targeted drugs.

Key words: colorectal cancer, leucovorin, LV, phase II, S-1

introduction

Recently, the development of irinotecan and oxaliplatin in combination with 5-fluorouracil (5-FU)-based regimens has led to significant improvement of survival in patients with metastatic colorectal cancer (mCRC). Various phase III studies of first-line chemotherapy have reported combination therapy with i.v. 5-FU/leucovorin (5-FU/LV) plus oxaliplatin (FOLFOX regimen) or 5-FU/LV plus irinotecan (FOLFIRI regimen) as a standard regimen for mCRC [1–4]. Recent clinical trials have examined whether oral fluoropyrimidines such as uracil–tegafur (UFT)/LV and capecitabine could be a replacement for i.v. 5-FU/LV. A combination of capecitabine and oxaliplatin (XELOX regimen) was found not to be inferior to FOLFOX in terms of progression-free survival (PFS) [5]. The standard treatment of mCRC is consequently shifting from 5-FU/LV-based regimens, which require central venous access, to more convenient oral-based care.

S-1 is a capsule preparation combining FT, an oral 5-FU derivative, with gimeracil (CDHP) and oteracil potassium (Oxo) at a molar ratio of 1.0 : 0.4 : 1.0. CDHP reversibly inhibits the activity of dihydropyrimidine dehydrogenase (DPD), a metabolizing enzyme of 5-FU. Oxo inhibits the activity of orotate phosphoribosyltransferase and is distributed in high concentrations in the gastrointestinal (GI) tract, where it suppresses GI disorders caused by 5-FU.

In Japan, S-1 was approved for the treatment of gastric cancer in 1999 and was subsequently approved for the treatment of colorectal cancer (CRC), head and neck cancer, non-small-cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, and biliary tract cancer. Recently, several phase III studies have established S-1 as a standard treatment of gastric cancer, including postoperative adjuvant chemotherapy [6–8]. Two phase II studies of S-1 were conducted in patients with mCRC. Single-agent S-1 was shown to be very effective, with high response rates (36% and 40%) and good median survival times (MSTs) (12 months) for at

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the time these studies were conducted given the lack of second-line therapies available [9, 10].

LV is known to enhance the efficacy of 5-FU by inhibiting thymidylate synthase. A meta-analysis consisting of >3000 patients' clinical data revealed that LV improves response rates and overall survival (OS) when combined with 5-FU, as compared with 5-FU alone [11]. Oral UFT/LV has been shown to be as effective as i.v. 5-FU/LV (Mayo regimen), with significantly favorable safety profile against metastatic disease [12, 13]. In an adjuvant setting, oral UFT/LV regimen was demonstrated to be as effective as i.v. 5-FU/LV (Roswell Park Memorial Institute regimen) in patients with curatively resected stage II/III colon cancer [14]. On the other hand, addition of oral LV to another fluoropyrimidine, capecitabine, leads to increased GI toxicity or hand–foot skin reaction, with no enhancement of response [15].

In a phase I study of oral LV plus S-1 in patients with mCRC, recommended treatment schedule with fixed dose of S-1 and LV was determined. S-1 and LV were administered twice a day at a daily dose of 80–120 mg for S-1, a conventional dose of S-1, and 25 mg for LV. The dose (schedule)-limiting toxic effects (DLTs) were mainly GI symptoms such as grade 3 stomatitis/pharyngitis, nausea, diarrhea or ileus, and exanthema. The response rate was 67% (10 of 15). The recommended treatment schedule was 2 weeks of administration followed by 2 weeks of rest [16]. To evaluate the safety and efficacy of a combination of S-1 and LV (S-1/LV regimen) given in the recommended schedule, we conducted a phase II study in chemotherapy-naïve patients with mCRC.

patients and methods

patient selection

Eligible patients had histologically confirmed CRC; have at least one measurable lesion; adequate oral intake; aged 20–74; no previous treatment of metastatic disease (adjuvant chemotherapy was allowed if finished 180 days before enrollment); an Eastern Cooperative Oncology Group performance status of zero to two; adequate bone marrow, liver, and renal functions as follows: a serum hemoglobin concentration of ≥9.0 g/dl, a white blood cell count of 4000–12 000/mm^3, a neutrophil count of ≥2000/mm^3, a platelet count of ≥100 000/mm^3, a serum total bilirubin concentration of ≤1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase concentrations of ≤100 IU/l, a serum alkaline phosphatase level of less than twice the upper limit of the normal institutional level (ULN), and a serum creatinine level of less than ULN; and written informed consent. Patients were excluded from this study if they had a contraindication for S-1; a history of serious hypersensitivity to LV; an active infection; serious concomitant diseases or conditions (intestinal obstruction, pulmonary fibrosis, heart failure, renal failure, liver failure, etc.); severe ascites or pleural effusion; extensive bone metastasis; brain metastasis or symptoms of brain metastasis; diarrhea (watery stools); or another synchronous cancer. We also excluded patients participating in other clinical studies; women who were pregnant, nursing infants, possibly pregnant, or planning to become pregnant; and men who were intending to conceive children.

treatment plan

S-1 (capsules containing 20 or 25 mg of FT) and LV (25-mg tablets) were provided by Taiho Pharmaceutical Co., Ltd, Tokyo, Japan. The dose of S-1 was determined according to body surface area as follows: <1.25 m^2, 40 mg; 1.25–1.50 m^2, 50 mg; and ≥1.50 m^2, 60 mg. LV was given at a fixed dose of 25 mg each time. S-1 and LV were given together orally twice a day for two consecutive weeks, followed by 2 weeks rest. This 4-week cycle was repeated until the onset of disease progression or unacceptable adverse events. No pretreatment was allowed. The dose of S-1 could be decreased by one level in the event of the following toxicity: grade 4 leucopaenia or thrombocytopaenia; grade 4 non-hematologic toxicity; or grade 3 diarrhea, stomatitis, skin conditions, or febrile neutropaenia that did not resolve with symptomatic treatment. The dose of LV could not be decreased.

toxicity and response criteria

Laboratory and clinical examinations were carried out within 15 days before enrollment, every 1 week during the first course of treatment and every 2 weeks from the second course onward. Tumors were evaluated on the basis of computed tomographic scans and serum carcinoembryonic antigen levels within 30 days before enrollment and every 4–6 weeks after the start of treatment. In the assessment of the best overall response, a complete response (CR: the disappearance of all lesions and normalization of tumor marker level) or partial response (PR: at least a 30% decrease in the sum of the longest diameter of all measured lesions taking as reference the baseline sum longest diameter) had to continue for at least 4 weeks and to be confirmed. A best overall response of stable disease (SD: neither sufficient shrinkage to quality for PR nor sufficient increase to qualify for PD taking as reference the smallest sum longest diameter since the treatment started) required no evidence of progressive disease (PD: at least a 20% increase in the sum of the longest diameter of all measured lesions taking as reference the smallest sum longest diameter recorded since the treatment started or the appearence of new lesion) for at least 6 weeks after the start of treatment. Response to S-1/LV treatment was externally reviewed and analyzed. Tumors were assessed according to RECIST criteria. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0).

statistical analysis

The response rate in previous phase II studies of S-1 alone in patients with CRC was 33% [42 of 129; 95% confidence interval (CI) 25–41]. Therefore, the threshold rate of response to the S-1/LV regimen was set at 30%, and the expected response rate was estimated to be 50%, which was ~20 percentage points higher than the response rate for S-1 alone. Assuming that the response rate follows a binomial distribution, we calculated the number of patients required to obtain the expected response rate (given a threshold response rate of 30%), with a one-sided test, a significance level of 2.5% ($\alpha/2 = 2.5\%$), and a statistical power (1-β) of 80%. We estimated that a target sample size of 54 patients would be needed to reject the null hypothesis with a power of 80%.

The Kaplan–Meier method was used to estimate time to progression (TTP), time to treatment failure (TTF), and OS. All data obtained until the completion of the study period were included in the safety analyses. Clinical cut-off date for this study was 25 June 2008.

The study was approved by the institutional review board at each participating center. For the duration of the study, an independent data-monitoring committee monitored safety. The study was undertaken in accordance with the Helsinki Declaration and Japanese Good Clinical Practice Guidelines.

results

patient characteristics

From October 2005 through June 2006, a total of 56 patients were enrolled from 12 hospitals: all were eligible. Patient characteristics are described in Table 1. A total of 406 courses of

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Table 1. Patient characteristics

Characteristics	N = 56	
	n	%
Gender		
Male	30	54
Female	26	46
Age, years		
Median	62	
Range	32–72	
ECOG performance status		
0	53	95
1	3	5
2	0	0
Primary site		
Colon	32	57
Rectum	24	43
Histologic grading		
Well differentiated	20	36
Moderately differentiated	29	52
Poorly differentiated	5	9
Mucinous	2	4
Site of metastases		
Liver	39	70
Lung	26	46
Lymph nodes	24	43
Peritoneum	3	5
Other	7	13
No. of sites evaluated		
1	24	43
2	20	36
3	8	14
4	2	4
≥5	2	4
Prior adjuvant therapy		
Yes	10	18
No	46	82
Hemoglobin (g/dl)		
Median	12.50	
Range	9.0–16.8	
Alkaline phosphatase (IU/l)		
Median	280.0	
Range	137–1408	

ECOG, Eastern Cooperative Oncology Group.

the study treatment cycles were delivered to patients. The median number of treatment courses was 6 (range 1–26). The median treatment period was 5.1 months (range 0.3–29.4). The median relative dose intensity was 81% (range 43–109) for S-1 and 93% (range 49–113) for LV.

response to therapy

The response rate, which was the primary end point of this study, was evaluated in all 56 patients. No patient had a complete response, but 32 had PRs, 16 had stable disease, and 8 had progressive disease. The response rate was 57% (95% CI 43–70) (Table 2). The median time to response was 1.9 months (range 0.9–5.3).

Table 2. Tumor response

	N = 56	
	n	%
Complete response	0	0
Partial response	32	57
Stable disease	16	29
Progressive disease	8	14
Not evaluable	0	0
Overall response rate (%)	32	57
95% CI	43.2–70.3	
Time to progression, months		
Median	6.7	
95% CI	5.4–7.9	

Tumor response was externally assessed according to the RECIST criteria. CI, confidence interval.

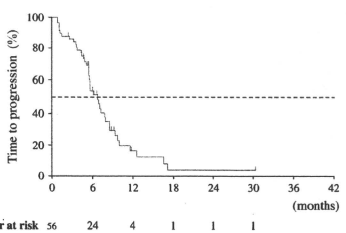

Figure 1. Kaplan–Meier curve of time to progression.

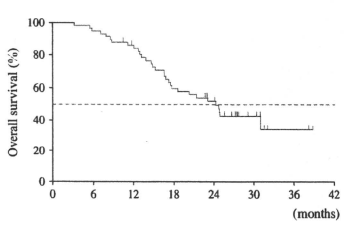

Figure 2. Kaplan–Meier curve of overall survival.

With a median follow-up time of 27.2 months, the median TTP was 6.7 months (95% CI 5.4–7.9) (Figure 1). The median TTF was 6.0 months (95% CI 5.4–7.8). The MST was 24.3 months (95% CI 17.5–XXX; upper bound of 95% CI was not estimable) (Figure 2) with the survival rate of 86% at 1 year and 52% at 2 years. Second-line treatment, including curative or palliative surgery, was given to 52 (93%) of the 56 patients, among whom 36% received oxaliplatin-based chemotherapy and 41% received irinotecan-based chemotherapy (Table 3).

Table 3. Further treatment after study chemotherapy

	$N = 56$	
	n	%
Oxaliplatin based	20	36
Irinotecan based	23	41
Surgery		
Curative	3	5
Palliative	2	4
None	4	7
Other	4	7

Table 4. Hematological and non-hematological adverse events

	$N = 56$		
	All grade (%)	Grade 3 (%)	Grade 4 (%)
Leucopaenia	31 (55)	0	0
Neutropaenia	36 (64)	8 (14)	0
Anemia	35 (63)	2 (4)	0
Thrombocytopaenia	14 (25)	1 (2)	0
AST	17 (30)	0	0
ALT	20 (36)	1 (2)	0
Bilirubinaemia	25 (45)	1 (2)	0
Nausea	42 (75)	1 (2)	0
Vomiting	20 (36)	1 (2)	0
Stomatitis	49 (88)	11 (20)	0
Abdominal pain	18 (32)	0	0
Diarrhea	46 (82)	18 (32)	0
Fatigue	48 (86)	0	0
Anorexia	48 (86)	12 (21)	0
Weight loss	21 (38)	1 (2)	0
Rash	33 (59)	1 (2)	0
Skin exfoliation	21 (38)	0	0
Hand–foot syndrome	4 (7)	0	0
Pigmentation disorder	50 (89)	0	0
Lacrimation increased	18 (32)	1 (2)	0
Dysgeusia	31 (55)	0	0

Numbers are patients who reported events. Severity was graded according to the CTCAE, version 3.0.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

safety assessment

The most frequent common adverse events are shown in Table 2. Grade 3 toxicity occurred in 35 patients (55%). There was no grade 4 toxicity. Grade 3 toxic effects with an incidence of ≥10% were given to diarrhea (32%), anorexia (21%), stomatitis (20%), and neutropaenia (14%) (Table 4).

The dose had to be decreased at least once in 33 patients (59%). The median number of treatment courses until the dose of S-1 was initially decreased was 2 (range 1–4). The main reasons for dose reductions were diarrhea, stomatitis, and rash. Rest periods were prolonged in 53.6% of the patients, mainly because of diarrhea, stomatitis, and rash, similar to the reasons for dose reductions.

The median times to the onset of diarrhea, stomatitis, and rash were 15 days (range 1–169), 12 days (range 3–201), and 8 days (range 3–148), respectively. The median times to the worst grade of these toxic effects were 20 days (range 1–769), 14 days (range 5–237), and 10 days (range 3–148), respectively. The median times from the worst grade to the resolution of these toxic effects were 7 days (range 1–29), 10 days (range 2–79), and 10 days (range 1–70), respectively.

The reasons for the withdrawal of treatment were mainly disease progression (86%). Withdrawal due to toxic effects was rare (4%) and there were no treatment-related deaths.

discussion

This phase II trial was conducted to evaluate the response rate of the S-1/LV regimen in patients with previously untreated mCRC. All 56 enrolled patients were eligible. S-1/LV regimen yielded promising results, without combination with oxaliplatin, irinotecan, or molecular-target agent as first-line treatment. The response rate, the primary end point of this trial, was 57%. With a median follow-up time of 27.2 months, the median TTP was 6.7 months, the MST was 24.3 months, and survival rates were 86% at 1 year and 52% at 2 years. In previous phase II studies of single-agent S-1, the response rate was 35%–40%, the median TTP was 5.3 months, and the MST was 12 months. In these studies, S-1 was given for 4 weeks, followed by 2 weeks of rest [9, 10]. In our study, the S-1 combined with LV was clearly more effective than S-1 alone, despite a shorter treatment period (2 versus 4 weeks). The antitumor activity of 5-FU is thought to involve the following mechanism: 5-fluoro-2′-deoxyuridine-5′-monophosphate, a metabolite of 5-FU, forms a ternary complex with thymidylate synthase and 5,10-methylenete terahydrofolate, a metabolite of LV. This complex inhibits thymidylate synthase, thereby blocking DNA synthesis [17]. In our study, enhancement of the antitumor activity of S-1 by oral LV is ascribed to this mechanism.

UFT is a derivative of 5-FU which is the same as S-1 and is a compounding oral agent of FT and uracil. *In vitro*, CDHP has been shown to inhibit DPD activity 180-fold higher than uracil [18]. In the previous pharmacokinetic (PK) studies, there was difference in PK profile about 5-FU between S-1 and UFT. Compared with UFT, S-1 showed longer maximum plasma concentration time (T_{max}) (3.5 versus 1.1 h), lower maximum plasma concentration (C_{max}) (128.5 versus 265 ng/ml) and longer half-time ($T_{1/2}$) (1.9 versus 0.34 h). The area under the curve (AUC) of 5-FU were 723.9 ng·h/ml for S-1 ($AUC_{0-14\ h}$) and 338 ng·h/ml for UFT ($AUC_{0-8\ h}$) [19, 20]. In this study, S-1/LV regimen demonstrated higher response rate and longer TTP compared with previously reported UFT/LV [12, 13]. Although these comparisons are limited in value, it was considered that these differences were due to the difference in the inhibitory effect of DPD.

In phase III studies of 5-FU/LV reported in the past decade or so, response rates were 10%–30%, with a PFS/TTP of 4.5–6.0 months. Response rates with FOLFOX or FOLFIRI range from 30% to 55%, with a PFS/TTP of 7.0–8.5 months [21, 22]. XELOX regimen showed response rates of 48% and a PFS of 7.1 months [23]. Although there is limitation to

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compare due to the differences in study population between this study (Asians) and referred studies (Western countries), the S-1/LV regimen has one of the highest response rates, despite the absence of oxaliplatin and irinotecan, among currently available regimens not including molecular-targeted drugs such as bevacizumab. The efficacy profiles of S-1 seemed to be generally better in Asian studies than that of others; however, it remained still unclear whether this difference was due to ethnic difference or good selected study population.

Recent clinical trials in patients with mCRC have not only compared treatment regimens but also examined strategies for subsequent treatment. The capecitabine, irinotecan, and oxaliplatin (CAIRO) trial compared sequential chemotherapy (first-line capecitabine, second-line irinotecan, and third-line capecitabine plus oxaliplatin) with combination chemotherapy (first-line capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin). OS did not differ significantly between sequential chemotherapy and combination chemotherapy [hazard ratio (HR) = 0.92; 95% CI 0.79–1.08; $P = 0.33$ by the log-rank test]. Sequential therapy was thus considered a valid treatment option for mCRC [24]. The 5-FU, oxaliplatin, and irinotecan: use and sequencing (FOCUS) trial, compared three different strategies of sequential and combination chemotherapy in patients with unresectable mCRC: single-agent 5-FU (given with levofolinate), followed by single-agent irinotecan (strategy A, control group); 5-FU, followed by combination chemotherapy (strategy B); and combination chemotherapy from the outset (strategy C). Compared with strategy A, strategy B did not significantly prolong survival (HR = 0.94; 95% CI 0.84–1.05; $P = 0.24$ by the log-rank test), whereas strategy C did (HR = 0.88; 95% CI 0.79–0.98, $P = 0.02$ by the log-rank test). There was no significant difference in survival between strategy B and strategy C (HR = 1.06; 90% CI 0.97–1.17). The FOCUS trial concluded that maximum tolerable treatment should be used as first line in the noncurative setting, and the staged approach of initial single-agent treatment upgraded to combination was not inferior to first-line combination therapy. This was an alternative option for discussion with patients [25]. At present, sequential therapy is recognized as a useful alternative for combined therapy.

After the study treatment, 93% of the patients in our study were given subsequent therapy. Of the 56 patients, 36% received oxaliplatin-based chemotherapy, 41% received irinotecan-based chemotherapy, and 5% underwent curative surgery. At the time of starting this trial, neither the FOLFOX nor the FOLFIRI regimen and no bevacizumab was approved in Japan. Grothey et al. [26] found that 5-FU, oxaliplatin, and irinotecan contributed to prolonged survival. In fact, Tournigand et al. [21] reported that survival exceeded 20 months in patients with mCRC who were enrolled in a crossover study of FOLFOX and FOLFIRI. The good survival in our study seems to be attributed to three reasons. First, the relatively recent approval of the FOLFOX and FOLFIRI regimens for use in Japan increased options for subsequent treatment. Secondly, the S-1/LV regimen, an intensive treatment that does not include oxaliplatin or irinotecan, was given as first-line therapy. Thirdly, the S-1/LV regimen was associated with a low rate of treatment withdrawal due to toxicity and a high rate of subsequent therapy; consequently, a high proportion of patients were able to receive sequential chemotherapy.

As for safety, there was no grade 4 toxicity or treatment-related mortality in our study. Common non-hematologic toxic effects included pigmentation, stomatitis, anorexia, fatigue, diarrhea, nausea, rash, and taste disorders. The incidences of grade 3 diarrhea, anorexia, and stomatitis were 32%, 21%, and 20%, respectively. Although these rates are higher than those reported for single-agent S-1 or standard chemotherapy, these toxic effects did not raise treatment discontinuation. The median number of courses until the first decrease in the dose of S-1 was 2 (range 1–4). The dose was decreased in 33 patients (59%). The main reasons for decreases in dose were stomatitis (11 patients), diarrhea (11 patients), and rash (nine patients). Mucositis characterized by stomatitis and diarrhea was considered the DLT of the S-1/LV regimen. Observed DLT was shifted from hematological toxicity to GI toxicity when S-1 was administered with LV. The median time to the onset of the worst grade of diarrhea and stomatitis was 14–20 days after the start of treatment. These toxic effects resolved after 7–10 days. Our experience indicates that toxicity associated with the S-1/LV regimen is manageable by appropriately reducing the dose of S-1 or by extending the rest period between treatment courses. So the S-1/LV regimen was generally well tolerated, with an acceptable toxicity profile.

Both S-1 and LV are administered orally, so this regimen does not require a central venous port. Patients therefore have to spend less time on follow-up visits, and the convenience of oral administration makes the S-1/LV regimen extremely useful clinically. Another advantage is the low incidence of hand–foot syndrome, the most common toxicity of capecitabine, another oral fluoropyrimidine.

In phase I/II studies of S-1 combined with oxaliplatin (SOX regimen), S-1 was given for 2 weeks at the conventional dose in Japan, similar to our S-1/LV regimen, followed by 1 week of rest. Oxaliplatin (130 mg/m^2) was given on day 1, within a 3-week cycle. The SOX regimen was very effective, with a response rate of 50% and a median PFS of 6.4 months. The most common toxicity of grade 3 or higher was thrombocytopaenia, typically associated with oxaliplatin [27]. Since the DLT of S-1/LV regimen was mucositis such as diarrhea and stomatitis, the combination with oxaliplatin, the toxicity profile of which does not overlap with that of S-1/LV, may be more appropriate than irinotecan for the treatment of metastatic disease requiring intensive chemotherapy. The preliminary results of a phase I study evaluating the S-1/LV regimen plus oxaliplatin have been reported. S-1/LV was given for 1 week followed by 1 week of rest, and oxaliplatin was given every 2 weeks (SOL regimen). The S-1/LV regimen was administered at the standard dose in Japan; the recommended dose of oxaliplatin was determined to be 85 mg/m^2. In that phase I study, five (83%) of the six patients who received the recommended dose of S-1, LV, and oxaliplatin had PRs. DLTs (grade 3 diarrhea and grade 3 hypertension) occurred in one of the six patients [28]. As for combinations of S-1 and irinotecan, a phase III study is going on to compare survival between the FOLFIRI regimen and S-1 plus irinotecan (IRIS

regimen), given as second-line treatment. The results are scheduled to be available in the near future.

Our results indicate that the S-1/LV regimen is a promising treatment of mCRC. On the basis of these preliminary data, further clinical trials of S-1/LV-based chemotherapy are going on. After the completion of these trials, phase III studies are promptly required to validate the clinical usefulness of S-1/LV-based chemotherapy.

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disclosures

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ORIGINAL ARTICLE

LEARNING CURVE FOR ENDOSCOPIC SUBMUCOSAL DISSECTION OF LARGE COLORECTAL TUMORS

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Background and Aim: No studies have previously described the learning curve for colonic endoscopic submucosal dissection (ESD). The aim of the present study was to describe the learning curve for ESD of large colorectal tumors based on a single colonoscopist's experience.

Methods: ESD was carried out for 120 colorectal tumors in 115 patients (68 males, median age 70 years). All procedures were carried out by a single experienced colonoscopist. The cases were grouped chronologically into three periods: (1st): cases 1–40; (2nd): cases 41–80; and (3rd): cases 81–120.

Results: The learning curve was the changes in proficiency over time. Proficiency was expressed as procedure time per unit area of specimen. In the 1st, 2nd and 3rd periods, the proficiencies were 18.9, 12.6 and 12.9 (min/cm^2), respectively. The proficiencies in the 2nd and 3rd periods were significantly shorter than in the 1st period (*t*-test, $P < 0.05$). The en-bloc resection rates of the 1st, 2nd and 3rd periods were 92.5% (37/40), 90% (36/40) and 97.5% (39/40), respectively. The en-bloc and R0 resection rates of the 1st, 2nd and 3rd periods were 85% (34/40), 77.5% (31/40) and 92.5% (37/40), respectively. The perforation rates of the 1st, 2nd and 3rd periods were 12.5% (5/40), 5% (2/40) and 5% (2/40), respectively.

Conclusion: Based on our analysis of the learning curve, approximately 80 procedures must be carried out to acquire skill with ESD for large colorectal tumors. However, approximately 40 procedures were sufficient to acquire skill in avoiding perforations during the ESD procedure.

Key words: colorectal cancer, colorectal tumor, endoscopic mucosal resection, endoscopic submucosal dissection, learning curve.

INTRODUCTION

Laterally spreading tumors (LST) are recognized as one of the primary lesions that progresses to invasive colorectal cancer.[1] Because these lesions typically extend laterally rather than vertically, endoscopic mucosal resection (EMR) appears to be an appropriate therapy.[1,2] However, for large colorectal tumors, conventional injection and snare EMR methods tend to result in piecemeal resections, and local recurrences frequently occur.[3–6] Some studies reported that subtypes of the LST tended to invade the submucosal layer.[2,7] One subtype was the granular type of LST (LST-G) with large nodules (mixed type) and another subtype was the non-granular type of LST (LST-NG) with depressed areas. LST-NG was reported to particularly favor multi-focal invasions, and the invasion area is difficult to estimate before treatment.[7] Therefore, en-bloc resection is considered an ideal approach for precise pathological assessment and prevention of local recurrences.[8]

Recently, Japanese pioneers developed endoscopic submucosal dissection (ESD) for large colorectal tumors.[9–11] In some large scale studies, most of the target lesions for ESD were LST.[12–15] Outcomes of ESD showed excellent rates of en-bloc resection and local recurrence compared to conventional EMR.[16] Conversely, ESD presented problems associated with long procedure times and high perforation rates.[16,17] Furthermore, ESD for colorectal tumors requires superior endoscopic skills compared to all other types of therapeutic endoscopy. Hence, it is important to develop guidelines for acquiring proficiency in colonic ESD. To this end, some authors analyzed learning curves for ESD in the treatment of early gastric cancers.[18,19] However, no previous studies have analyzed learning curves in colonic ESD. The aim of the present study was to describe the learning curve for the ESD of large colorectal tumors, based on the analysis of a single colonoscopist's experience.

METHODS

Patients

Endoscopic submucosal dissection was carried out for a total of 120 colorectal tumors in 115 patients (68 males, median age 70 years) at Saku Central Hospital in Nagano, Japan between June 2003 and September 2008. All the procedures were performed by a single experienced colonoscopist (K.H.) who had performed approximately 2500 colonoscopies, 500 colonic endoscopic mucosal resections and 20 upper gastrointestinal ESD. All cases were grouped chronologically into three periods as follows: 1st: cases 1–40; 2nd: cases 41–80; and 3rd: cases 81–120. In the first 20 cases,

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the procedures were carried out under the guidance of an expert in upper gastrointestinal ESD (T.O.). During this period, another 10 cases of colorectal ESD were carried out in live demonstration seminars by the faculties of other hospitals. These cases had similar characteristics of included cases. Selection of cases for live demonstration seminars mainly depended on the timing of reservations.

Proficiency was measured as procedure time divided by the tumor area. The area of a resected specimen was approximately oval. All measurements were evaluated retrospectively from our database for every period, including clinicopathological features, procedure time per unit area of specimen (min/cm^2), en-bloc resection rate, en-bloc and R0 resection rate, and the perforation rate. The R0 resection was defined as a complete resection that showed negative lateral and vertical margins in a pathological diagnosis. We carried out the present study in accordance with the guidelines of our institutional review board. Informed consent was obtained from all patients before treatment.

Indication for ESD

Endoscopic submucosal dissection was indicated for large colorectal tumors (>20 mm) that were expected to present difficulty in an en-bloc resection with the conventional EMR technique. LST-NG >20 mm and LST-G >30 mm were considered to be particularly good indications for ESD.[20] Before treatment, a magnified chromoendoscopic observation was carried out: a finding of submucosal massive invasion (invasive pattern) was considered a contraindication for ESD.[21] An invasive pattern that was characterized by an irregular, distorted pit pattern in a demarcated area suggested that the submucosal invasion was larger than 1000 μm.[21]

ESD procedure

In the 1st period, we used a pediatric-type colonoscope (PCF-Q240ZI; Olympus Optical Co., Tokyo, Japan) with a hand-made water jet system and an attachment.[22] After the 2nd period, we used a newly developed pediatric-type colonoscope with a built-in water jet system (PCF-Q260JI; Olympus Optical Co.) and an attachment. Also, after the 2nd period, a carbon dioxide (CO_2) insufflation system was used instead of air insufflation.[23] In all periods, a sodium hyaluronate solution was used for submucosal injection.[10,24] Also, in all periods, we used a high-frequency generator unit (ICC200 or VIO300D; Erbe Elektromedizin, Tübingen, Germany). Mucosal incisions were made with a flex knife[11,25] (Olympus Optical Co.) and a flush knife[26] (Fujifilm Co., Saitama, Japan). A hook knife[25,27,28] (Olympus Optical Co.) was used primarily for submucosal dissections and for part of the mucosal incision, in combination with the flex knife and flush knife. The hook knife was also used for hemostasis during submucosal dissection.[29]

Statistical analysis

Data were evaluated with the *t*-test and the chi-squared test. Analyses were carried out with the Stat Mate package ver.3 for Windows (ATMS, Tokyo, Japan). Calculated *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 115 patients with 120 lesions were enrolled into the study. To determine the changes in skill level over time, the cases were grouped chronologically into three periods. The clinicopathological features are shown in Table 1. In all periods, the majority of lesions were on the right side of colon, and rectal lesions comprised 20–30% of all lesions. There were no statistically significant differences in lesion location among the three periods. A large majority of macroscopic features comprised LST-NG and LST-G. The combined observations of LST-NG and LST-G (mixed type) comprised two-thirds of all lesions. There were no significant differences in the macroscopic features among the three3 periods. In every period, cancers comprised a majority of all lesions. There were no significant differences in pathological features among the three periods. In all periods, the mean tumor size was >30 mm. In the 2nd period, the mean tumor size (40.2 mm) was significantly larger than the means observed in the 1st and 3rd periods (*t*-test, $P < 0.05$).

The mean procedure time of all cases was 141 min (range: 22–595 min). The mean procedure times of the 1st, 2nd and 3rd periods were 159, 145 and 118 min, respectively. To correct for the differences in tumor size among periods, the proficiency was calculated as the procedure time per square centimeter of specimen area (min/cm^2). The learning curve was the change in the proficiency over time as demonstrated in Fig. 1. The proficiencies in the 1st, 2nd and 3rd periods were 18.9, 12.6 and 12.9 (min/cm^2), respectively. The proficiencies in the 2nd and 3rd periods were significantly shorter than that of the 1st period (*t*-test, $P < 0.05$).

The en-bloc resection rate, en-bloc and R0 resection rate, and perforation rate of all cases were 93.3% (112/120), 85% (102/120) and 7.5% (9/120), respectively. The learning curves for improving the outcomes of colonic ESD are shown in

Table 1. Clinicopathological features of the colorectal tumors

	1st period	2nd period	3rd period
Location			
Right side	24	24	24
Left side	3	5	7
Rectum	13	11	9
Macroscopic appearance			
LST-NG	17	11	17
LST-G (mixed type)	9	17	11
LST-G (homogeneous type)	12	12	11
Miscellaneous	2	0	1
Pathological features			
Adenoma	18	15	14
M-Ca	18	21	16
SM-Ca (SM > 1000 μm)	4 (0)	4 (1)	10 (5)
Mean tumor size (mm) (range)	31.3 (6–100)	40.2 (15–95)	33.2 (11–72)

Left side, descending and sigmoid colon; LST-G, laterally spreading tumor, granular type; LST-NG, laterally spreading tumor, non-granular type; M-Ca, mucosal cancer; right side, cecum, ascending and transverse colon; SM-Ca submucosally invasive cancer.