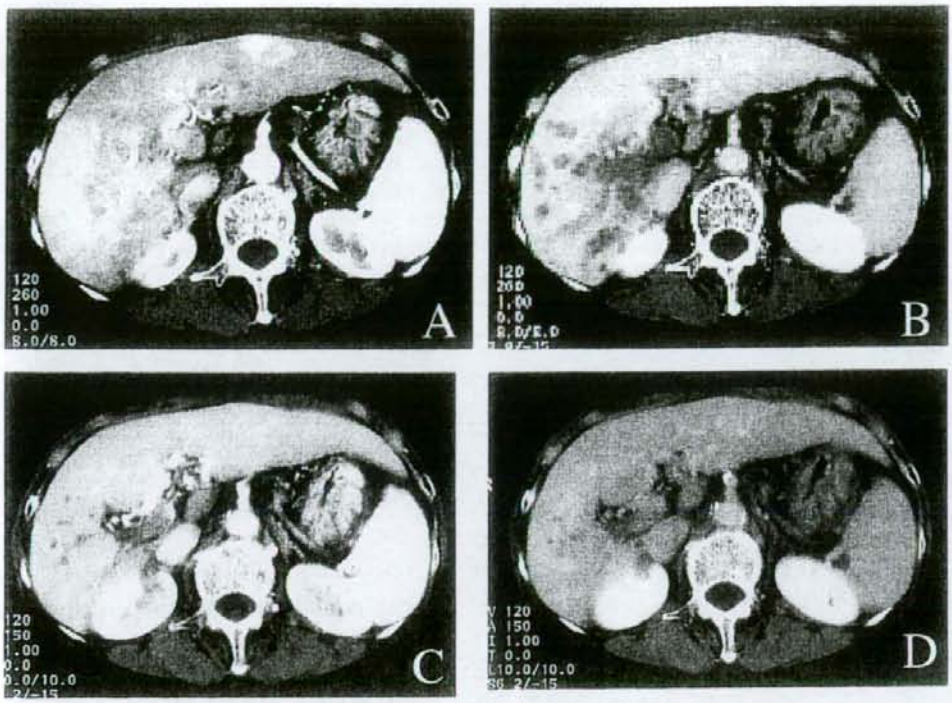

Fig. 1 Abdominal computed tomography (CT) scans before chemotherapy showed diffuse hepatocellular carcinoma in the right lobe of the liver with tumor emboli in the trunk of the portal vein (A—B). 2 months after the start of chemotherapy, CT scans showed improved HCC with tumor emboli (C—D) Early phase of enhanced CT scans (A, C). Delayed phase of enhanced CT scans (B, D).

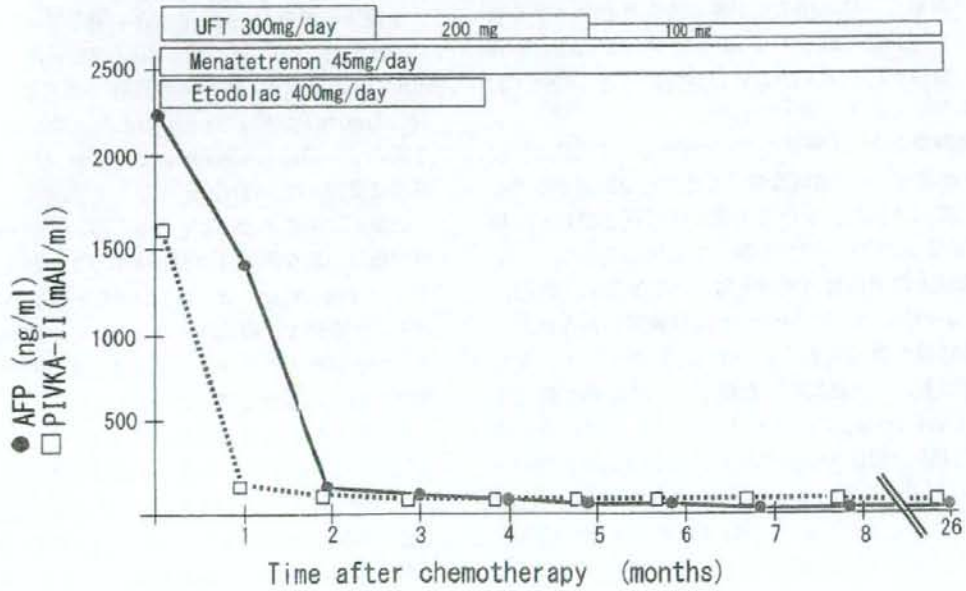

Fig 2 Time course of alpha-fetoprotein and PIVKA II after the start of chemotherapy.

食思不振や下痢などの症状は経過中みられなかった．UFT投与開始から1カ月後には，AST 60 U/l，ALT 23 U/l，PT 61.3%，Alb 3.2 g/dl と入院時に比して肝機能の増悪がみられたが，投与4カ月後にはAST 22 U/l，ALT 14 U/l，PT 79.0%，Alb 4.0 g/dl と腫瘍の縮小と共に改善がみられた．その後も肝機能はほぼ正常であり，Child-Pugh分類では現在までAを維持している．

UFTは血球減少などのため2.5カ月後より200 mg/日，5カ月後より100 mg/日へ減量し，現在は100 mg/日で維持している．etodolacは右季肋部から右側腹部にかけての自発痛が消失したため4カ月後に中止した．ビタミンK_2 45 mg/日は現在まで投与量を変えずに継続している．この症例においては，腫瘍の縮小状態の維持には少量のUFTで充分であると考えられるが，ビタミンK_2がこれに関与したかどうかは不明である．

日本肝癌研究会の肝癌治療直接効果判定基準[3,4]に従って治療効果をまとめると，直接治療効果度（TE）は3であり，新病巣はみられず，門脈腫瘍塞栓の明らかな退縮がみられた．AFPは2220 ng/ml から3 ng/ml，PIVKA IIは1590 mAU/ml から11 mAU/ml に低下している（それぞれ治療前，治療開始後6カ月）．PSも2から0に改善した．総合評価はpartial response（PR）であった．以上のように治療開始2カ月で効果を認め，その後現在（治療開始後2年2カ月）まで特別な自覚症状はなく，発病前とほぼ同様に日常生活をされている．

考　案

患者は初診時すでに肝右葉にびまん性に肝細胞癌が浸潤し，門脈腫瘍塞栓を伴っていたため，外科的切除，局所療法，肝動脈塞栓療法は不可能な状態であった．また高齢に加え腫瘍によると思われる倦怠感のため，急速に全身状態が悪化しつつあった．JIS scoreおよび全身状態からは予後不良と考えられた．このため経口抗癌剤であるUFTを開始した．

UFTはuracilとtegafurがモル比4：1からなる合剤である．UFTの抗腫瘍活性はtegafurの代謝産物である5-fluorouracilによるものであり，uracilは5-fluorouracilの分解を阻害するとされている．さらにYonekuraらは，UFTとその代謝産物であるγ-hydroxybutyric acidとγ-butyrolactoneが，tumor angiogenesisを抑制することを実験的に示した[5]．Tanakaらはstage Iの非小細胞肺癌において，vascular endothelial growth factor（VEGF）が高発現している群ではUFTの有効性が高く，UFTのtumor angiogenesis抑制効果を臨床的にも示した[6]．Stage IV-Aの肝細胞癌患者においてUFTの投与はその生存率を上げることが報告されているが[7]，一般的に肝細胞癌に対してUFT単独での治療効果は低率であると考えられる[8]．しかしながら進行肝細胞癌に対する有効例も散見され[9～11]，門脈腫瘍塞栓を伴う進行した肝細胞癌に対してUFTが著効したとの症例報告もみられる[12～14]．

本例ではCOX-2阻害剤（etodolac）を疼痛に対して，ビタミンK_2（menatetrenone）を骨粗鬆症に対して，UFTとほぼ同時に投与を開始した．

ビタミンK_2は以前より培養肝細胞癌細胞株に対して増殖抑制効果があることが報告されており[15]，その機序に関しては現在も解明のための実験が続けられている[16]．また臨床的にはPIVKA-IIが肝細胞癌患者の門脈腫瘍塞栓発生の予測因子になること[17]や，肝硬変患者にビタミンK_2を投与すると肝細胞癌の発生が有意に低くなることが報告されている[18]．

非ステロイド性消炎鎮痛剤（non-steroidal anti-inflammatory drugs：NSAIDs）は，cyclooxygenase（COX）を阻害することにより消炎鎮痛作用を発揮すると考えられている．COXには恒常的に発現しているCOX-1と，刺激により誘導されるCOX-2がある．NSAIDs（COX阻害剤）による大腸癌の発生抑制に関しては，すでに多くの疫学的，実験的検討にて明らかになっているが[19,20]，これらの機序にはCOX依存性とCOX非依存性のシグナル伝達経路の抑制が考えられている．肝細胞癌においても，とくにCOX-2阻害剤の抗腫瘍効果は培養細胞レベルで検討されており，その機序としてCOX-2阻害剤が細胞周期やMAP kinaseの経路に関わる蛋白質の発現や活性を調整することや[21,22]，COX阻害剤がperioxysome proliferator-activated receptor γ（PPAR γ）のagonistとして作用することが考えられている[23,24]．

ビタミンK_2とCOX-2阻害剤（etodolac）に関して，上述のように肝細胞癌に対する実験的な抗癌作用を示す成績はあるが，臨床的には抗癌作用を示す文献報告はなく，これまでの症例報告に従えば，本例もUFT単独により奏効した可能性が高いと考えられる．しかしビタミンK_2とetodolacが，UFTの抗癌作用に何らかの影響を与えた可能性も否定できないと考えている．

患者はRCサイン陽性の食道静脈瘤がみられたが，治療経過中に食道静脈瘤は軽快している．これは治療による門脈腫瘍塞栓の縮小と，腫瘍塞栓周囲の側副血行

路の発達によると考える．

経過中に胃潰瘍S1がみられたが，UFTやCOX-2阻害剤(etodolac)の副作用は否定できないと考える．とくにetodolacは，従来の非ステロイド性消炎鎮痛剤に比して消化性潰瘍の副作用の頻度は少ないと考えられているが，etodolacにはCOX-2阻害作用に加えCOX-1阻害作用もあること，また選択的COX-2阻害剤によっても少ないながら消化管粘膜障害が生ずることから[25]，たとえCOX-2阻害作用が優位であっても，NSAIDs使用中における消化管障害の発生の可能性には常に注意が必要である．

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A case of advanced hepatocellular carcinoma with tumor emboli in the portal vein showing marked reduction after oral adminisration of UFT, etodolac and Vitamin K_2

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A 78-year old Japanese woman positive for anti-hepatitis C virus antibody was referred to our hospital because of general fatigue, weight loss and high levels of α-fetoprotein (AFP) and protein induced by Vitamin K absence or antagonist II (PIVKA-II). After examinations, she was diagnosed as having advanced hepatocellular carcinoma (HCC) with tumor emboli in the portal vein. Severe esophageal varices due to portal vein tumor thrombi were observed. Oral administration of uracil-tegafur (UFT) was initiated at the dose of 300 mg/day. HCC in the liver, portal vein tumor thrombi and esophageal varices were remarkably reduced after chemotherapy. The patient has been alive with good quality of life for more than 26 months. Etodolac and vitamin K_2 were initiated with UFT at the same time. We suppose that etodolac and vitamin K_2 may have contributed to antineoplastic effect of UFT in this case.

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Original Article

Moderate Neutropenia with S-1 Plus Low-dose Cisplatin May Predict a More Favourable Prognosis in Advanced Gastric Cancer

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ABSTRACT:

Aims: **The effects of haematological adverse events on the prognosis of patients with gastric cancer were investigated.**

Materials and methods: **We retrospectively analysed the association between haematological adverse events and prognosis in 23 patients with far advanced or recurrent gastric cancer treated with a JFMC27-9902 regimen consisting of an oral fluorouracil derivative S-1 plus low-dose cisplatin.**

Results: **The patients who suffered grade 2–3 neutropenia ($n = 10$; median survival time [MST] 679 days) were found to have significantly more favourable prognoses than patients who developed grade 0–1 ($n = 10$; MST 271 days) or grade 4 neutropenia ($n = 3$; MST 408 days) ($P = 0.0039$ and 0.0112, respectively), although no significant differences were found among the clinicopathological factors of any grade groups. With respect to anaemia or thrombocytopenia, there were no significant differences among the MSTs of the groups stratified by toxicity grade. Multivariate survival analysis revealed that grade 2–3 neutropenia is an independent predictor of a more favourable prognosis (hazard ratio = 38.693, $P = 0.0004$).**

Conclusions: **These results suggest that S-1 plus low-dose cisplatin against gastric cancer may contribute to long survival when it induces moderate neutropenia. Nakata, B. *et al.* (2006). *Clinical Oncology* 18, 678–683**

Key words: Chemotherapy, neutropenia, prognosis, stomach neoplasm

Introduction

Recently it has been reported that haematological toxicity due to chemotherapy is a prognostic factor in breast cancer [1–3]. To the best of our knowledge, however, there has been no investigation to predict the prognosis of patients with gastric cancer by the chemotherapeutic adverse events.

The novel oral fluorouracil derivative S-1 was approved for the treatment of gastric cancer by the Ministry of Health, Labor, and Welfare of Japan in 1999. The post-marketing survey showed that adverse events of grade 3 or more occurred in 3808 cases at the following rates: neutropenia 6.1%, anaemia 4.6%, thrombocytopenia 1.5%, anorexia 5.9%, fatigue 3.5%, nausea/vomiting 2.2%, diarrhoea 2.0%, stomatitis 1.2%, pigmentation 1.1% [4]. Therefore, incidences of severe toxicities including neutropenia of S-1 alone are very low. S-1 with low-dose cisplatin has recently come to be considered one of the most noteworthy regimens for advanced gastric cancer [5–8]. Recently, the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) conducted a phase I trial entitled JFMC27-9902 in which S-1 plus low-dose cisplatin was given to patients with unresectable or recurrent gastric cancer [9]. The 23 enrolled patients were closely assessed for toxicity. Hence, the toxic profile data were deemed suitable for research into the relationship between adverse effects and survival benefit. In the present retrospective study, univariate and multivariate survival analyses were employed to determine the prognostic effect of haematological adverse events induced by chemotherapy.

Patients and Methods

Treatment Regimen

The details of the treatment regimen have been described previously [9]. The regimen was given under informed

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consent and ethical approval. In brief, S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was given orally at a standard dose of 40 mg/m^2 twice daily after a meal. A course consisted of consecutive administration for 4 weeks followed by 2 weeks of rest. Low-dose cisplatin (1–6 mg/m^2 according to the dose escalation level) was given intravenously for five consecutive days followed by 2 days of rest during the period in which S-1 was being given. This combination therapy was given for no more than three courses (at least two courses) unless dose-limiting toxicity (DLT) occurred. Patient characteristics are described in Table 1.

Adverse Events

Blood counts were carried out at least once weekly. The grades of toxicity were evaluated using the National Cancer Institute Common Toxicity Criteria, version 2.0, based on the lowest recorded adverse events during any course of the regimen.

Statistics

In our previous report [9], the overall median survival time (MST) was 461 days (95% confidence interval 268–679 days), ranging from 34 to 958 days and using survival data up to 1 June 2003. In the present study, the cut-off date for survival analysis was 1 January 2004.

Statistical analyses were carried out using a Statistical Analysis System software (version 8.2, SAS Institute, Cary, NC, USA). We examined the MSTs of the combined grade groups (grade 0–1, grade 2–3 and grade 4) using the Log-rank test. Either the chi-squared test or Fisher's exact probability test was used to compare the prevalence or distribution of two variables, and the Student's t-test was employed to compare the mean age between two groups. Correlations of neutropenia grade with the cisplatin dosage, or the duration of treatment (course number), or other toxicities except neutropenia were evaluated using the Spearman rank correlation test. Multivariate survival analysis was carried out using the Cox proportional hazards model. $P < 0.05$ was considered to indicate statistical significance.

Results

Duration of Treatment

This combination was given for three courses in eight patients, two courses in nine patients and one course in four patients. The first course was stopped halfway for two patients. As described in our previous report [9], this regimen had been planned for two or three complete courses. Consequently, the accomplishment rate of this

Table 1 – Patient characteristics

Variable	Number of patients					
	Cisplatin (1 mg/m^2)	Cisplatin (2 mg/m^2)	Cisplatin (3 mg/m^2)	Cisplatin (4 mg/m^2)	Cisplatin (6 mg/m^2)	Total
Gender						
Male	2	3	6	3	4	18
Female	1	3	0	0	1	5
Age (years)						
30–39	0	0	1	0	0	1
40–49	0	1	0	0	1	2
50–59	3	1	0	1	0	5
60–69	0	3	4	2	2	11
70–75	0	1	1	0	2	4
Performance status						
0	2	3	5	3	2	15
1	1	3	1	0	1	6
2	0	0	0	0	2	2
Diagnosis						
Unresectable	2	3	5	2	5	17
Recurrent	1	3	1	1	0	6
Histological differentiation						
Well/moderate	2	2	3	2	2	11
Poor/signet ring cell	1	4	3	1	3	12
Hepatic metastasis						
Negative	2	5	3	1	3	14
Positive	1	1	3	2	2	9
Peritoneal metastasis						
Negative	2	2	5	2	4	15
Positive	1	4	1	1	1	8

S-1 (80 mg/m^2) was given to all patients.

regimen was 74% (17/23). Six patients could not be treated completely. The reasons for which the regimen was stopped before finishing one or two courses for these patients were as follows: grade 4 neutropenia (two patients), grade 3 anorexia (two patients), grade 4 diarrhoea (one patient), treatment-unrelated toxicity (dermatomyositis; one patient). As shown, haematological toxicity was rarely responsible for shortening the regimen or reducing the total administration of S-1 and cisplatin.

Survival Data Stratified by Haematological Toxicity

The overall MST of all patients was 449 days (95% confidence interval 275–621 days), ranging from 34 to 1074 days. Table 2 shows the effect of haematological toxicity on survival. With respect to neutropenia grade, there was a significant difference between the MSTs of the grade 0–1 group and those of the grade 2–3 group (Fig. 1). A significant difference was also observed between the MSTs of the grade 4 group and the grade 2–3 group (Fig. 1). However, there was no significant difference between the MSTs of the grade 0–1 group and the grade 4 group. The clinicopathological factors of these groups were not significantly different, as shown in Table 3.

Regarding anaemia and thrombocytopenia, no significant differences in survival time among toxicity grade groups were observed (Table 2).

Multivariate Survival Analysis for the Effects of Neutropenia and Clinicopathological Factors on Survival

Recurrent disease and grade 0–1 or grade 4 neutropenia were found to be independent indicators of the least favourable prognosis by multivariate survival analysis (Table 4).

Correlation of Neutropenia Grade with Other Factors Affecting Treatment Effect

There was no relationship between the neutropenia grade and the cisplatin dosage (Fig. 2). No correlation between the neutropenia grade and the duration of treatment (course number) was observed (Spearman rank correlation test; $\rho = 0.141$, $P = 0.5071$). There were moderate relationships of the neutropenia grade between anaemia and thrombocytopenia grade (Table 5). However, there were no correlations between the neutropenia grade and non-haematological toxicity grade (Table 5).

Discussion

When a chemotherapy regimen causes no adverse effects, it may be inducing no anti-tumour effects because of an insufficient dose of the anti-cancer agent. On the other hand, severe adverse effects during chemotherapy not only impair the patient's quality of life, but also provide only low efficacy due to incomplete execution of the regimen. In the JFMC27-9902 phase I study, DLT was defined as the occurrence of grade 4 haematological toxicity or grade 3 non-haematological toxicity, and the maximum tolerated dose was defined as the dose level that produced DLT in 50% or more patients. The recommended dose was defined as the dose level that was one level under the maximum tolerated dose [9]. Such a protocol design is commonly executed in phase I studies to determine the most suitable dosages of chemotherapeutic agents without severe adverse toxicity. The dose defined in such a procedure becomes the starting dose of a regimen, which is probably

Table 2 – Relationship of survival to haematological toxicity grade

Toxicity	Grade	Number of patients	MST (days)	Range of survival time (days)	*P* value
Neutropenia	G0	6	271	34–958	0.0039 (G0–1 vs G2–3)
	G1	4	303	216–391	0.0112 (G2–3 vs G4)
	G2	2	NR	798–1026	0.5803 (G0–1 vs G4)
	G3	8	650	159–1074	
	G4	3	408	246–461	
	G0–1	10	271	34–958	
	G2–3	10	679	159–1074	
Anaemia	G0	4	565	268–958	0.2169 (G0–1 vs G2–3)
	G1	7	621	97–1026	– (G2–3 vs G4)
	G2	8	382	34–1074	– (G0–1 vs G4)
	G3	4	318	159–731	
	G4	0	–	–	
Thrombocytopenia	G0	12	333	34–798	0.2474 (G0–1 vs G2–3)
	G1	4	482	357–1026	0.1768 (G2–3 vs G4)
	G2	3	958	449–1074	0.1326 (G0–1 vs G4)
	G3	3	408	159–731	
	G4	1	246	246	

G, grade; MST, median survival time; NR, not reached.

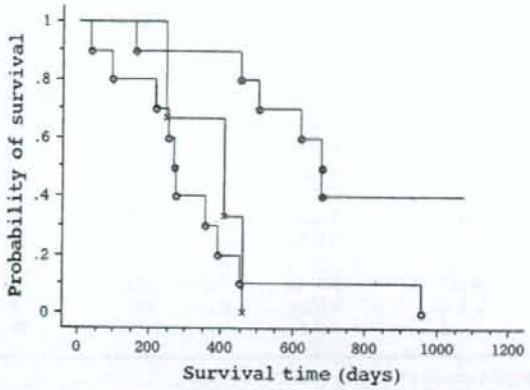

Fig. 1 — Probability of survival in patients with far advanced gastric cancer treated with S-1 plus low-dose cisplatin in relation to their neutropenia grade. ○, Grade 0–1; ●, grade 2–3; ×, grade 4. There were significant differences between the median survival times of the patients with grade 2–3 and grade 0–1 neutropenia ($P = 0.0039$) and grade 2–3 and grade 4 neutropenia ($P = 0.0112$).

safe and effective for most patients. In actual clinical use, however, the doses of chemotherapeutic agents are usually adjusted, or 'tailored', for each individual patient according to observed adverse events [10,11].

Recent retrospective studies on breast cancer suggest that patients who experience at least some degree of neutropenia during their adjuvant chemotherapy may show a more favourable survival rate [1–3]. Saarto *et al.* [1] showed that stage II/III breast cancer patients with grade 2 or 3/4 leukopenia during adjuvant chemotherapy (cyclophosphamide, doxorubicin and oral tegafur with or without tamoxifen) showed significantly better long-term disease-free and overall survival rates, compared with those with grade 0 or 1 leukopenia. Additionally, Mayers *et al.* [2] reported that breast cancer patients experiencing grade 3/4 myelosuppression during a cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen had a better outcome than those without such toxicity. Furthermore, Cameron *et al.* [3] showed that breast cancer patients who were treated with adjuvant CMF and who experienced grade 2–3 neutropenia had a significantly better prognosis than those with either grade 0–1 or 4 neutropenia. These findings prompted us to investigate how the degree of adverse effects is associated with prolonged survival in gastric cancer treated with chemotherapy.

Notwithstanding differences in cancer sites and chemotherapeutic regimens from these previous studies, we observed similar results in gastric cancer patients treated with S-1 plus low-dose cisplatin. Specifically, patients experiencing grade 2–3 neutropenia showed a significantly longer survival rate than those who developed grade 0–1 or

Table 3 — Comparison of clinicopathological factors between neutropenia grade 0–1, 2–3 and 4 groups

Clinicopathological factor	Neutropenia grade			*P* value
	G0–1	G2–3	G4	
Gender				
Male	8	8	2	>0.9999 (G0–1 vs G2–3)
Female	2	2	1	>0.9999 (G0–1 vs G4)
				>0.9999 (G2–3 vs G4)
Age				
	59.5 ± 8.7	59.9 ± 10.6	64.0 ± 14.2	0.9277 (G0–1 vs G2–3)
				0.5054 (G0–1 vs G4)
				0.5944 (G2–3 vs G4)
Performance status				
0	5	9	1	0.1393 (G0–1 vs G2–3)
1	4	1	1	0.6119 (G0–1 vs G4)
2	1	0	1	0.0776 (G2–3 vs G4)
Diagnosis				
Unresectable	9	6	2	0.3034 (G0–1 vs G2–3)
Recurrent	1	4	1	0.4231 (G0–1 vs G4)
				>0.9999 (G2–3 vs G4)
Hepatic metastasis				
Negative	7	5	2	0.6499 (G0–1 vs G2–3)
Positive	3	5	1	>0.9999 (G0–1 vs G4)
				>0.9999 (G2–3 vs G4)
Peritoneal metastasis				
Negative	7	7	1	>0.9999 (G0–1 vs G2–3)
Positive	3	3	2	0.5105 (G0–1 vs G4)
				0.5105 (G2–3 vs G4)

G, grade. *P* values were calculated using the chi-squared test (fisher's exact probability test) for all clinicopathological factors except age. *P* value for age was calculated using Student's t-test.

Table 4 — Multivariate analysis of independent prognostic factors in far advanced gastric cancer treated with S-1 plus low-dose cisplatin by the Cox proportional hazards model

Variable	Coefficient	Standard error	*P* value	95% CI	Hazard ratio
Gender (female vs male)	1.838	0.982	0.0612	0.917–43.030	6.281
Age (years) (61 ≤ vs 60 ≥)	0.606	0.676	0.3699	0.487–6.895	1.833
Performance status (2–4 vs 0–1)	0.190	1.174	0.8713	0.121–12.082	1.210
Diagnosis (recurrent vs unresectable)	2.275	0.813	0.0051	1.976–47.875	9.727
Histological differentiation (poor/signet ring cell vs well/moderate)	−0.016	0.626	0.9790	0.289–3.353	0.984
Hepatic metastasis (positive vs negative)	−1.215	0.681	0.0746	0.078–1.128	0.297
Peritoneal metastasis (positive vs negative)	−1.550	0.810	0.0556	0.043–1.038	0.212
Neutropenia (grade 0–1/4 vs grade 2–3)	3.656	1.040	0.0004	5.037–297.217	38.693

CI, confidence interval. The cut-off value for age was the mean age (60.3 years) of the patients studied here.

4 neutropenia (Table 2, Fig. 1), without significant differences among the clinicopathological factors of any groups (Table 3). Moreover, multivariate survival analysis indicated that both grade 2–3 neutropenia and recurrent disease were independent predictors for long-term survival (Table 4). It was speculated that moderate neutropenia after chemotherapy might be a barometer of the appropriate chemotherapeutic dosage for the individual to derive a sufficient anti-tumour effect without severe adverse effects, resulting in an improved duration of survival.

It may be concerned with whether there were any correlations between the neutropenia grade and the factors affecting the treatment effect, including dose intensity. Cisplatin dosage did not affect the neutropenia grade (Fig. 2). The duration of treatment also did not correlate with the neutropenia grade. S-1 dosage was fixed in this regimen. Therefore, S-1 dose intensity did not affect the neutropenia grade. It is reasonable that myelotoxicities such as neutropenia, anaemia and thrombocytopenia were correlated with each other to some extent (Table 5). However, anaemia and thrombocytopenia were not the reasons for stopping the regimen within two courses. High-grade anorexia and diarrhoea were the main DLTs in this regimen. Moreover, non-haematological toxicities, including nausea/vomiting, stomatitis and fatigue, deteriorate quality of life and cause incomplete execution of the regimen, resulting in the low chemotherapeutic effect. However, no associations between the neutropenia grade and those non-haematological toxicities were observed (Table 5). These data indicated that the neutropenia grade was independent of the factors affecting the treatment efficacy.

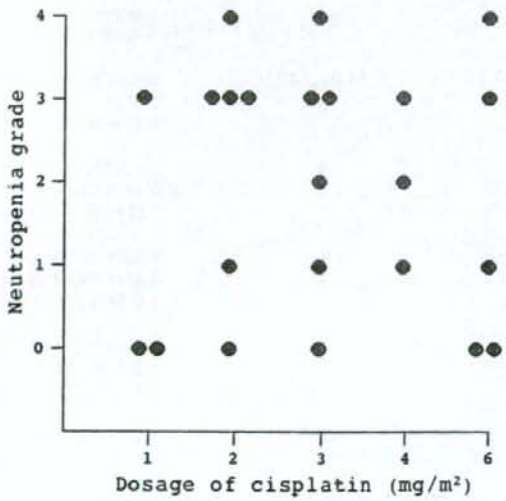

Fig. 2 — Correlation between neutropenia grade and cisplatin dosage. There was no correlation between the two values by the Spearman rank correlation test ($\rho = 0.014$, $P = 0.9489$).

In conclusion, the use of neutropenia grade as a guideline might be effective at helping to achieve optimal survival benefits in chemotherapy using S-1 plus low-dose cisplatin for gastric cancer. However, this study was a pilot study using a small number of patients, and further research using larger numbers of patients and other chemotherapeutic regimens for gastric cancer is necessary to obtain definitive results.

Table 5 — Relationship of neutropenia grade to other toxicity grade

Toxicity	ρ	*P* value
Anaemia	0.426	0.0457
Thrombocytopenia	0.588	0.0058
Anorexia	−0.151	0.4782
Fatigue	−0.162	0.4479
Nausea/vomiting	−0.343	0.1074
Diarrhoea	0.007	0.9729
Stomatitis	0.121	0.5708
Skin	0.074	0.7270
Hepatotoxicity	−0.048	0.8237
Nephrotoxicity	0.120	0.5735

P value was calculated using the Spearman rank correlation test.

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A phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma

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Abstract

Background: Unresectable biliary tract carcinoma is known to demonstrate a poor prognosis. We conducted a single arm phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) for advanced biliary tract malignancies basically on an outpatient basis.

Methods: Between February 1996 and September 2003, 42 patients were enrolled in this trial.

LFP therapy: By using a total implanted CV-catheter system, 5-FU (160 mg/m^2/day) was continuously infused over 24 hours for 7 consecutive days and CDDP (6 mg/m^2/day) was infused for 30 minutes twice a week as one cycle. The administration schedule consisted of 4 cycles as one course. RESIST criteria (Response evaluation criteria for solid tumors) and NCI-CTC (National Cancer Institute-Common Toxicity Criteria) (ver.3.0) were used for evaluation of this therapy. The median survival time (MST) and median time to treatment failure (TTF) were calculated by the Kaplan-Meier method.

Results: Patients characteristics were: mean age 66.5(47–79): male 24 (54%): BDca (bile duct carcinoma) 27 GBca (Gallbladder carcinoma) 15: locally advanced 26, postoperative recurrence 16. The most common toxicity was anemia (26.2%). Neither any treatment related death nor grade 4 toxicity occurred. The median number of courses of LFP Therapy which patients could receive was two (1–14). All the patients are evaluable for effects with an over all response rates of 42.9% (95% confidence interval C.I.: 27.7–59.0) (0 CR, 18 PR, 13 NC, 11 PD). There was no significant difference regarding the anti tumor effects against both malignant neoplasms. Figure 2 Shows the BDca a longer MST and TTF than did GBca (234 vs 150, 117 vs 85, respectively), but neither difference was statistically significant.

The estimated MST and median TTF were 225 and 107 days, respectively. The BDca had a longer MST and TTF than GBca (234 vs 150, 117 vs 85, respectively), but neither difference was statistically significant.

Conclusion: LFP therapy appears to be useful modality for the clinical management of advanced biliary tract malignancy.

Background

Biliary tract cancers are rare in North America, with approximately 8,000 new cases diagnosed in 2003 [1]. However, bile duct carcinoma (BDca) and gallbladder carcinoma (GBca) are not rare in northern Japan [2], Taiwan [3], and South Korea [4]. In Japan, these malignancies are the sixth leading cause of cancer deaths, and in 1999, there were 8,557 deaths from BDca and 6,340 deaths from GBca [5]. As an surgical resection of the primary tumor and the areas of local extension remains the most effective therapy [6], even for non-curative operations [7]. However, in over 75% of the patients whose disease is locally advanced or already metastatic cases, the median survival time for patients receiving only the best possible supportive care is only about 6 months [1]. Furthermore, there is a high rate of both local and systemic recurrence, even after a curative resection [1,6]. As a result, an effective chemotherapy for biliary malignancy has been eagerly awaited. However, systemic single-agent chemotherapy has so far shown a poor efficacy [6,8], though many efforts has been done [9]. For example, the response rate of 5-fluorourasil (5-FU), cisplatin (CDDP), was 10–13%, and 8%, respectively [4], while new chemotherapeutic agents CPT-11, Gemsitabine, showed the poor response rate of 12.5% and 8%, respectively [3,4,10].

As a result, an effective combination chemotherapy has been eagerly anticipated. We spotlighted the combination of the two old anti-cancer agents, 5-FU, and CDDP.

In Japan, FP therapy combination of 5-FU continuous venous infusion (CVI) and low-dose consecutive CDDP (LFP) Therapy has been widely used since early 1990s for gastrointestinal advanced cancer [11,12]. Because of its low toxicity and relatively high response rate [13], LFP therapy has been widely used for the treatment of various unresectable advanced solid tumors, such as gastric cancer [14], hepatocellular carcinoma [15], pancreatic cancer [12], colon and head and neck [11]. Recent findings in experimental models have shown an additive or synergistic antitumor effects of LFP therapy. We observed that CDDP inhibited metionine transport into tumor cells, both in vitro and in vivo, with a synergic interaction by CDDP functioning as a modulator of 5-FU [11,12]. This synergistic effect was also associated with the induction of apoptosis [16] and the p53 pathway [17,18].

Based on these findings, we conducted a single arm phase II study of LFP therapy in patients with advanced BDca and GBca.

Methods

Eligibility criteria

This study protocol was approved by the Kochi Municipal Central Hospital, Japan and written informed consent was obtained from all the patients. The patients were required to have unresectable locally advanced or metastatic disease of the biliary-tract or gallbladder advanced carcinoma with measurable lesions on a computed tomography (CT) scan. Other eligibility criteria included an age 18 years or more, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, estimated life expectancy of 12 weeks or more, adequate bone marrow function (leukocyte count > 3,500/μl, neutrophil count > 1,500/μl, and platelet count > 100,000/μl), bilirubin < 5.0 mg/dl, transaminases and alkaline phosphatase < 6 times upper limit of normal, and normal renal function tests (creatine level < 1.5 mg/dl, or creatinine clearance > 60 ml/min). No previous chemotherapy was permitted within 2 weeks. Radiotherapy and stenting to decompress the biliary tract was permitted. Patients with other clinically significant laboratory abnormalities, uncontrolled infection, concurrent severe medical problems unrelated to malignancy that would expose the patient to extreme risk, patients receiving another investigational drug within 30 days prior to study or receiving concurrent hormonal therapy, immunotherapy and those pregnant or lactating were excluded from the study. The study was conducted according to the Good Clinical Practices and the Declaration of Helsinki as amended in Hong Kong (1989).

Treatment plans

All patients were admitted to the hospital for about 10 days for a pretreatment evaluation, the first cycle treatment, and observation for adverse effects. If the degree of toxicity was within Grade 0–2, a second cycle of treatment or more were continued on an outpatient basis.

A pretreatment evaluation included complete medical history, physical examination, evaluation of performance status, urinalysis, chest radiograph, and diagnostic studies assessment such as CT scan. When the patient meets the eligibility criteria, central venous catheter system with a heparin coated catheter (Anthron PU catheter; TORAY™ and a port (Celcite brachial; TORAY™ or Vital port mini; COOK™) is implanted according to the method of Hata et al [19] prior to treatment.

The treatment plan involved the administration of 5-FU (160 mg/m^2/day) was continuously infused over 24 hours using a disposable infusion pump (7-day Infuser; Baxter™) and CDDP (3–6 mg/m^2/day) diluted with normal serine was infused for half an hour. Hydration was not needed. These doses were determined based on our experience of the previous LFP therapy for hepatocellular carcinoma [15]. The administration schedule consisted of 5-FU for 7 consecutive days and CDDP twice a week (day 1 and day 4) for each of four weeks as one treatment course. The treatment schedule and CV catheter system was

depicted on figure 1. Unless an exacerbation of the symptoms was observed, multiple courses of treatment were administered. When more than a grade 3 adverse effect was observed, a CDDP infusion was omitted and observed. If this omission was ineffective, 5-FU was also omitted. In case of hemoglobin < 8.0 g/dl, platelet count < 50,000/μl neutrophil count < 1,000/μl, blood transfusion of concentrated red blood cells (RBCs) or platelets, or granulocyte-stimulating factor (G-CSF) was applied.

We do not increase the dose of the anti-cancer agent during the chemotherapy protocol, even if the toxicity is low.

Toxicity and response evaluation

Complete blood counts twice a week and biochemical examinations were weekly carried out. Toxicity was evaluated based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) ver.3. The response was classified based on the Response Evaluation Criteria in Solid Tumors Guidelines (RECIST criteria) [20], taking into account the measurement of the longest diameter only for all target lesions: complete response (CR)-the disappearance of all target lesions; partial response (PR)-at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease (PD) -at least a 20% increase in the sum of the longest diameter of target lesions, taking as referenve the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; no change (NC)-neither sufficient shrinkage to quality for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started. Patients with a CR, a PR, an NC, or a PD required a confirmatory disease assessment at least one

Figure 1. ***Schedule for treatment and infusional method***

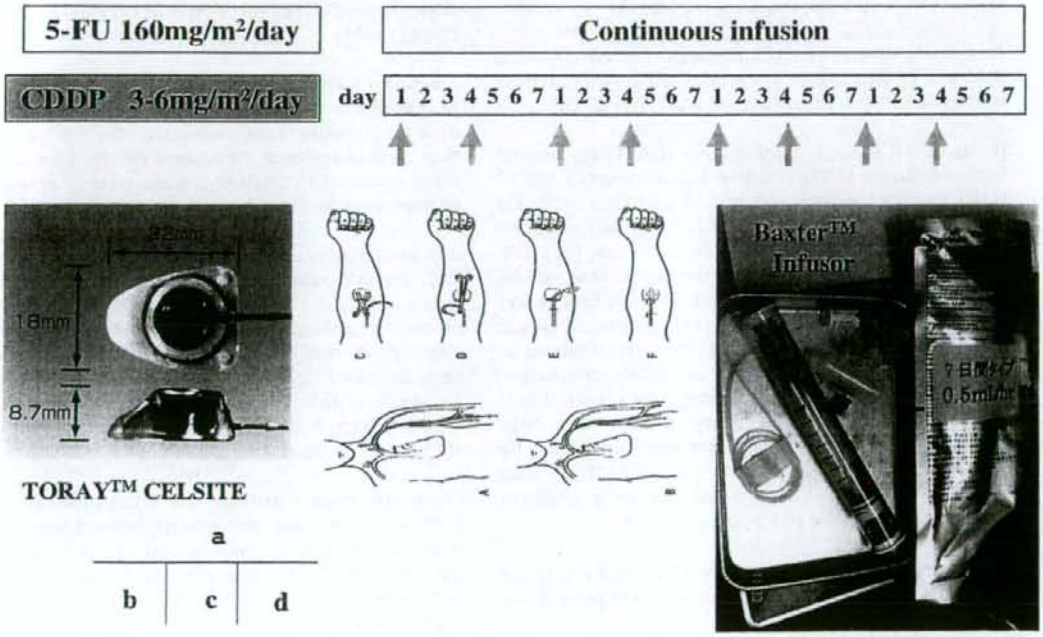

Figure 1

Schedule for treatment and infusional method. A schematic drawing of the chemotherapy schedule (a), and the Central Venous catheter system consists of PAS port (b), implantation technique (c) and portable infusion pump (d).

Figure 2. ***Survival and Treatment failure***

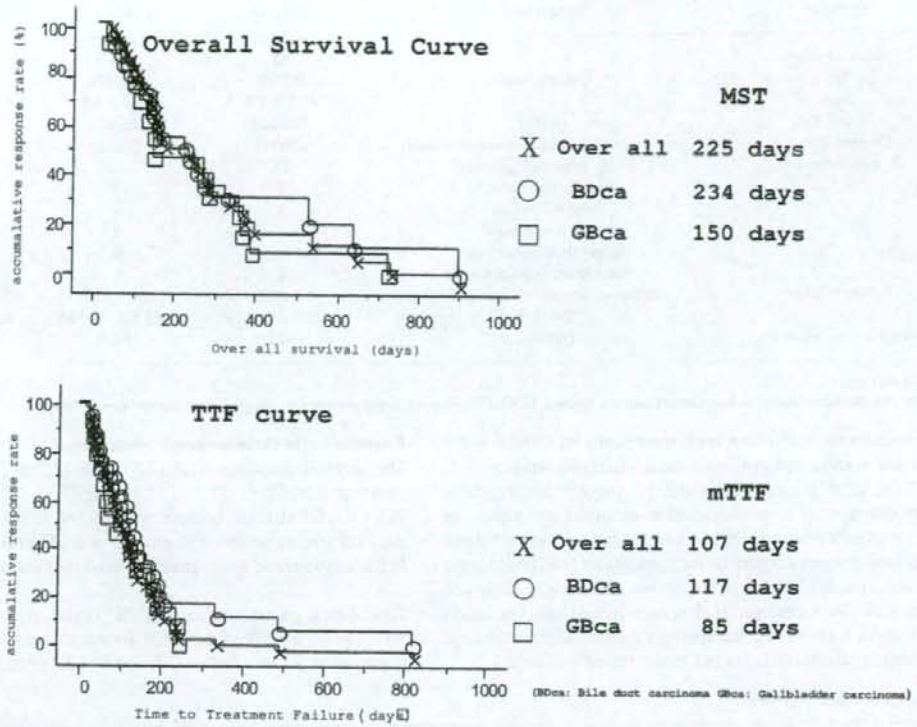

Figure 2

Survival and Treatment failure. Kaplan-Meier curves of Overall Survival (upper column) and Time to treatment failure (TTF) (lower column) are shown.

month later. Target lesions were evaluated by a plain and enhanced CT scan and plain chest X-ray for each course.

Statistical analyses

We used the Stat View J 5.0 software package (Abacus Concepts, Stat View. Abacus Concepts, Inc., Berkeley, CA, 1992–1998) for the statistical analysis. The time to Treatment Failure and the overall Survival Cumulative were obtained by the Kaplan-Meier method. The disease-free survival was compared by the Log rank test among the groups. Prognostic variables were evaluated by Cox's multivariate proportional hazard model. We defined the risk factors for LFP therapy for biliary tract malignancies in our study as significant factors based on both the Cox's and Kaplan-Meier's. A p value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

From February 1996 to December 2003, 42 patients were enrolled into the present study, and all were evaluable for efficacy and toxicity analyses. They consisted of 24 males and 18 females. The mean age was 66.5(47–79). The number of patients with BDca and GBca were 27 and 15, respectively. Twenty-six patients who were initially diagnosed to have biliary tract malignancies were not eligible for surgery because of locally advanced disease and/or metastasis (locally advanced). Another 16 patients had local recurrence and/or distant metastasis after surgery (postoperative recurrence). Disease extension was such that 11 patients (BDca: 7, GBca: 4), had only primary or local recurrence patients had only metastatic disease (BDca: 9, GBca: 5), another 17 patients (BDca:11, GBca: 6) had both diseases. Four patients had previously undergone

Table 1: Patient Characteristics

Variables	Startification	Over all	BDca	GBca
Spieces of cancer		42	27	15
Sex	(male/female)	(24/18)	(17/10)	(7/8)
Age		66.5 ± 7.5	64.8 ± 8.2	69.5 ± 4.7
ECOG PS	(0/1/2)	(36/4/2)	(22/4/1)	(14/0/1)
Disease Status	(unresectable/postoperative recurrence)	(26/16)	(15/12)	(11/4)
Disease extension	locally advanced (primary)	26	15	11
	local recurrence	7	7	0
	liver metastasis	9	4	5
	lung metastasis	4	3	1
	lymphnode metastasis	11	4	7
	miscellaneous metastasis	5	5	0
Tumor marker	carcinoembryonic antigen (CEA)	16.7 ± 60.7	6.4 ± 17.2	36.7 ± 100.5
	CA19-9	3035.5 ± 9507.6	4495.3 ± 11688.8	407.9 ± 587.2
Previous chemotherapy	(yes/no)	(4/38)	(3/24)	(1/14)

Abbreveations
BDca: bile duct carcinoma, GBca: Gallbladder carcinoma, ECOG PS: Eastern Cooperative Oncology Group performance status

chemotherapy, including such treatments as CDDP + VP-16, 5-FU + mitomycin C + farmorubicin, adriamycin + 5-FU. Two of 4 patients experienced surgery before these chemotherapy (i.e. postoperative recurrence). Seven of BDca patients had palliative radiotherapy. Three of these seven underwent surgery before radiation (i.e. postoperative recurrence). There were some differences between BDca and GBca on age, and serum tumor marker levels (CEA and CA19-9), but neither was statistically significant. The patient characteristics are enumerated in Table 1.

Response and time-to-event measures

The overall response rate (RR) was 42.9% (95% confidence interval C.I.: 27.7–59.0) with CR 0, PR 18, NC 13, PD 11, and clinical benefit was 73.8% (95% C.I.: 58.0–86.2). Patients with a PR, an NC or a PD required a confirmatory disease assessment at least two months later.

One GBca patient who got PR, could receive curative resection. The RR of primary lesion or locally advanced lesion was 50.0% (95% C.I.: 30.6–69.4), and the RR of

Table 2: Anti tumor effect

					Over all	
	CR	PR	NC	PD	Response Rate (%)95%C.I. CR+PR/TOTAL	Clinical Response (%)95%C.I. CR+PR+NC/TOTAL
Over all	0	18	13	11	42.9 (27.7–59.0)	73.8 (58.0–86.2)
BDca	0	11	10	6	40.7 (22.4–61.2)	77.8 (57.8–91.4)
GBca	0	7	3	5	46.7 (21.1–73.5)	66.7 (38.4–88.2)
					Primary or local recurrence	
	CR	PR	NC	PD	Response Rate (%)95%C.I. CR+PR/TOTAL	Clinical Response (%)95%C.I. CR+PR+NC/TOTAL
Over all	0	14	8	6	50.0 (30.6–69.4)	78.6 (59.0–91.7)
BDca	0	9	6	3	50.0 (26.0–74.0)	83.3 (58.6–96.5)
GBca	0	5	2	3	50.0 (18.6–81.4)	70.0 (34.7–93.5)
					Metastatic lesion	
	CR	PR	NC	PD	Response Rate (%)95%C.I. CR+PR/TOTAL	Clinical Response (%)95%C.I. CR+PR+NC/TOTAL
Over all	0	10	12	9	32.3 (16.7–51.4)	71.0 (52.0–85.8)
BDca	0	6	9	5	30.0 (11.8–54.3)	75.0 (50.9–91.4)
GBca	0	4	3	4	36.4 (10.8–69.3)	66.7 (30.7–89.2)

Abbreveations
BDca: bile duct carcinoma, GBca: Gallbladder carcinoma

Table 3: Toxicity

Hematological Toxicity	Gr1	Gr2	Gr3	Gr4	≧Gr3 (%)	Over all (%)
anemia	0	11	0	0	0 (0)	11 (26.2)
leukopenia	0	1	0	0	1 (0)	1 (2.3)
thrombocytopenia	0	2	3	0	3 (7.1)	5 (11.9)
Non-hematological Toxicity	**Gr1**	**Gr2**	**Gr3**	**Gr4**	**≧Gr3 (%)**	**Over all (%)**
nausea	3	4	1	0	1 (2.3)	8 (19.0)
vomiting	1	1	3	0	1 (2.3)	5 (11.9)
appetite loss	0	0	6	0	6 (14.3)	6 (14.3)
oral mucositis	0	4	0	0	0 (0)	4 (9.5)
taste disturbance	0	1	0	0	1 (2.3)	1 (2.3)
upper GI tract bleeding	0	1	0	0	0 (0)	1 (2.3)
diarrhea	1	0	0	0	0 (0)	1 (2.3)
general fatigue	0	1	1	0	1 (2.3)	2 (4.7)
jaundice	0	0	4	0	4 (9.5)	4 (9.5)
serum AST/ALT level elevation	0	4	1	0	1 (2.3)	1 (2.3)
Serum creatinine level elevation	0	6	0	0	0 (0)	6 (14.3)

metastatic lesions was 32.3%. Various RRs were demonstrated in Table 2. The responses of meatastatic lesions were as such; liver (CR:0, PR:6, NC:0, PD:3), lung (CR:0, PR:1 NC:3, PD:0), lymph node (CR:0, PR:3, NC: 6, PD2), miscellaneous (CR:0, PR: 2, NC: 2, PD: 1). There was no significant difference in terms of anti tumor effects against both malignant neoplasms. The overall MST was 225 days. The median TTF was 107 days. Figure 2 Shows the BDca a longer MST and TTF than did GBca (234 vs 150, 117 vs 85, respectively), but neither difference was statistically significant.

Toxicity

As shown in Table 3, neither any treatment related death nor grade 4 toxicity occurred. Overall, the most common toxicity was anemia occurring in 26.2% of patients followed by nausea (19.0%). The most frequent grade 3 toxicity was appetite loss (14.3%). The occurrence of ascites and jaundice may be partly because of the outcome of the disease progression.

Prognostic factors related survival and TTF

An analysis of a Cox proportional hazard model showed that no significant factor was found prognostic factors for either the overall survival or TTF (Table 4). However, the patients with LFP courses ≧2 had both a longer overall survival and TTF than those with LFP courses < 2 as depicted in Figure 3. The distribution of the patients with LFP courses ≧2 was (PR/NC/PD = 16/8/3), while that of those with LFP courses ≤2 was (PR/NC/PD = 2/5/8).

Table 4: Prognostic factors for over all survival and TTF

Stratification	Over all survival			Time to treatment Failure		
	Hazard ratio	p-value	95% C.I.	Hazard ratio	p-value	95% C.I.
Sex (male/female)	0.123	0.0128	0.024–0.640	0.225	0.0095	0.073–0.695
Age (≧69/<69)	0.634	0.6082	0.111–3.692	2.380	0.2269	0.583–9.713
ECOG PS (PS0/PS1/PS2)	0.016	0.0015	0.001–0.259	0.230	0.0007	0.001–0.152
Species of tumor (BDca/GBca)	0.095	0.0198	0.013–0.688	0.001	0.0411	0.0856–0.943
Disease status (locally advanced/postoperative recurrence)	0.121	0.0179	0.021–0.695	0.802	0.7388	0.001–0.152
Radiation (yes/no)	8.369	0.1491	0.467–150.112	0.603	0.4586	0.158–2.299
Previous chemotherapy (yes/no)	0.143	0.0255	0.016–1.241	0.495	0.4086	0.094–2.622
Initial CEA level (≧1 UL/<1 UL)	1.098	0.9053	0.234–5.160	2.453	0.1267	0.775–7.763
Interval decreasing CEA level (yes/no)	0.224	0.2859	0.014–3.499	1.734	0.5968	0.260–11.568
Initial CA19-9 level (≧5 UL/<5 UL)	0.078	0.0255	0.014–3.499	1.734	0.5968	0.260–11.568
Interval decreasing CA19-9 level(yes/no)	1.449	0.7667	0.125–16.774	0.326	0.2600	0.047–2.290

(Cox proportional hazard model)

Abbreviations

BDca: bile duct carcinoma, GBca: Gallbladder carcinoma, ECOG PS: Eastern Cooperative Oncology Group performance status, CEA: carcinoembryonic antigen, UL: upper limit

Figure 3. ***Relation between number of LFP courses and Over all survival and TTF***

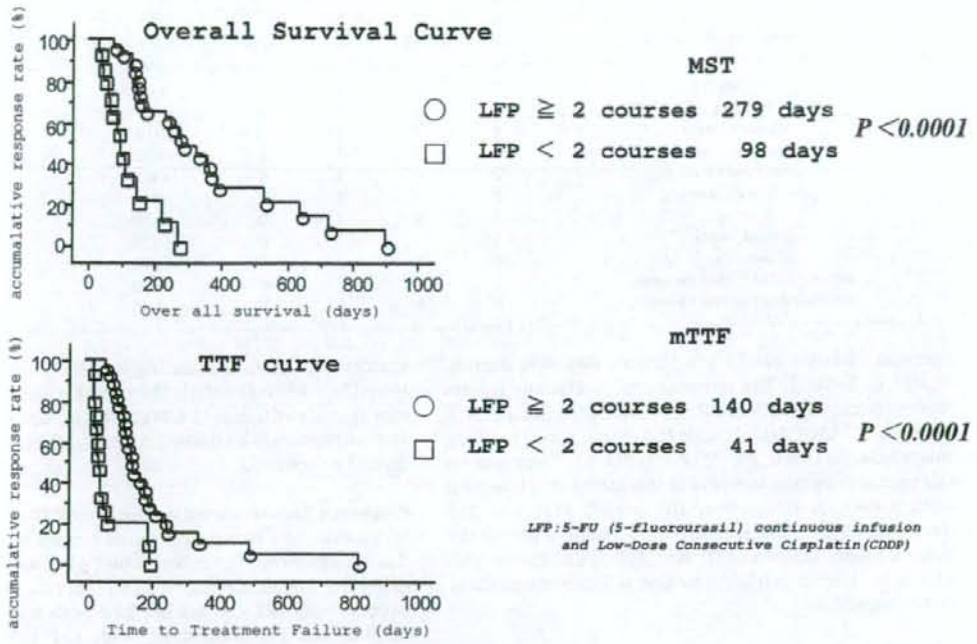

Figure 3

Relation between number of LFP courses and Over all survival and TTF. Differences by accomplished LFP (5-FU (5-fluorourasil) continuous infusion and Low-Dose Consecutive Cisplatin(CDDP)) courses are depicted regarding the overall Survival (upper column) and Time to treatment failure (TTF)(lower column).

Cost benefit

The difference between the inpatient-basis and the outpatient-basis or home treatment of this therapy in respect to cost is shown in Table 5. This was calculated based on the assumption that one patient received one-month treatment of this LFP therapy covered by Japanese National Health Insurance. The cost for outpatient-basis/home LFP therapy was approximately equivalent to 996 U.S. dollars which was about one-sixth less than the cost on an inpatient-basis.

Discussion

In the present study, we achieved an RR of 42.9% (95% C.I.: 27.7–59.0) with a median over all survival of 225 days and median TTF of 107 days. No grade 4 toxicity or treatment related death occurred. The cause of treatment failure of the other 37 patients was an aggravation of general condition due to primary disease, and not due to any adverse effect. LFP therapy showed a good compliance and the adverse effects were either tolerable or controllable.

The overall response rate of our study is relatively high for this type of tumor. However, our LFP method has achieved more than a 50% overall response rate in other tumors such as esophageal, gastric or colon cancers. Biliary tract cancer may be more malignant than other types of cancer.

One cycle of conventional LFP therapy consists of CDDP infusion consecutive five days per week and 24 hr continuous infusion of 5-FU consecutively 7 days per week [14].

Table 5: Cost-benefit

Outpatient-basis or home	Inpatient-basis
At home malignant tumor	Basic admission fee 472,900 yen
Administration fee 25,000 yen	Local infusion technical fee (addition to minute infusion) 46,200 yen
Portable infuser pump	
using fee 15,000 yen	Diet 63,600 yen
Medication	Medication
CDDP 20,000 yen	CDDP 20,000 yen
5-FU 15,000 yen	5-FU 15,000 yen
Tumor marker 5,000 yen	Tumor marker 5,000 yen
Other laboratory test 8,400 yen	Other laboratory test 8,400 yen
Imaging diagnosis 15,000 yen	Imaging diagnosis 15,000 yen
(antiemeric drug 16,000 yen)	(antiemeric drug 16,000 yen)
Total 103,600 (119,600) yen	Total 646,300 (662,300) yen

(One month treatment covered by Japanese National Health Insurance, A U.S. dollar is approximately equivalent to 104 Japanese yen)

Therefore, the patients were obliged to receive inpatient-basis treatment, which led to their inconvenience and a heavy burden due to the high admission fee. Regarding the five consecutive days of CDDP infusion, our preliminary study showed that CDDP infusion twice a week was sufficient to maintain the blood concentration of CDDP in order to achieve synergistic effect [15]. This fact and the application of a CV catheter system with PAS or vital port and portable infusion pump thus enable the patients to receive outpatient-basis treatment which is equivalent to the inpatient treatment in quality. As for central venous catheter, Knox reported six catheter infection cases occurred in 27 patients [6], but no complications related to the catheter system occurred in our study. Our good results were due to the easy technique of implantation associated with the catheter system [19]. In our hospital from July 1994 to December 2002, infection related to the CV-catheter system occurred in only 44 cases of total 1,350 implanted patients (3.4%).

We herein tried to compare our regimen with other combination chemotherapies [2,4-6,21-23] are summarized in Table 6. Our combination chemotherapy is thus considered to be effective enough to be recommended the biliary tract malignancy since our study achieved a low toxicity and high efficacy with a relatively higher RR and longer MST in comparison to these regimens. Kim's regimen [4] is also interesting since oral capesitabine was used. However, our results showed higher response rate and lower toxicity than Kim's.

Table 6: Current Combination Chemotherapy for Biliary tract cancer

Author (published year)	Number of Patients	Species of cancer	Regimen	RR (%)	MST (days)	mTTF (days)	Adverse effects (≧Gr3)	Treatment related death
Ishii(2004)	21	GBca	CEF(CDDP/5-FU/ epirubicin)	33.3	177*	-	hematological toxicity (52.3%)	none
	25	GBca	FAM(5-FU/Doxorubicin/ Mitomycin)	7.1		-	hematological toxicity (20%)	none
Lee (2004)	4	BDca	Gemsitabine/CDDP	50	270	150	thrombocytopenia (75%)	none
Doval(2004)	30	GBca	Gemsitabine/CDDP	36.6	140	126	nausea/vomiting (16%)	2
Malik(2003)	11	GBca	Gemsitabine/CDDP	64	294	196	anemia (45%)	none
Knox (2004)	27	BDca/ CBca	Gemsitabine/5-FU	33	159	111	hematological toxicity (11%)	none
Malik(2003)	30	CBca	Leucovorin/5-FU	7.5	444	141	diarrhea (30%)	1
Kim (2003)	42	BDca/ CBca	Capesitabine/CDDP	21.4	273	111	leucopenia (20%)	none

(* The result was overall survival of combined CEF and FAM)

Abbreveations

BDca: bile duct carcinoma, GBca: Gallbladder carcinoma, CDDP: Cisplatin, 5-FU: 5-fluorourasil, RR: response rate, MST: median survival time, mTTF: median time to treatment failure

One of the problems of our study was that the prognosis of the patients receiving less than two courses of LFP was remarkably poor as shown in Figure 3. Of these patients only one could receive second-line chemotherapy with CDDP/CPT-11. It is important to predict whether LFP therapy is effective or not. Fortunately, an effective method for predicting LFP therapy effectiveness for gastrointestinal cancers by detecting p53 has been reported [16-18]. This method may be applicable for biliary tract malignancy.

The present study used 5-FU continuous venous infusion (CVI) as an effector. If an oral drug which can help maintain a high blood concentration of 5-FU equivalent to or higher than that for the CVI-method exist, then the patients with biliary tract malignancy can avoid the need to use the catheter system but while still achieving an improved anti-tumor effect thus leading to an advanced quality of life. S-1 invented by one of the authors (T.S) [11] can thus be one of the candidates for this aim. S-1 is a novel oral fluoropyrimidine that consists of tegafur, which is a prodrug of 5-FU, 5-chloro-2, 4-dihydroxypyrimidine, which inhibits dihydropyrimidine dehydrogenase activity and potassium oxonate, which reduces gastrointestinal toxicity [11,24]. This feature helps to maintain a high blood concentration of 5-FU and less toxicity of digestive tract [11,24]. The result of 101 advanced gastric cancer patients with S-1 was reported to be 44.6% RR with 244 days of MST [25,26]. Furthermore, using the synergistic effect of LFP, the combination chemotherapy of CDDP and S-1 has also been performed for gastric cancer or pancreatic cancer at some institutes [13,25,27-30]. Many reports have so far described promising results. The application of low-dose CDDP and S-1 for biliary malignancies at our institute is now under consideration. Our study of LFP is thus considered to support the use of low-dose CDDP and S-1 regimen for BDca and GBca.

Conclusion

In conclusion, this outpatient-basis LFP therapy is considered to be appropriate as a first-line treatment for either advanced or recurrent biliary tract cancer and it promises to help improve the quality of life of cancer patients while also facilitating the clinical management of such patients.

Competing interests

The authors declares that they have no competing interests.

Authors' contributions

KK carried out this study, and drafted this manuscript. AT conceived the design of present study. SM participated in assessing radiological findings. TH participated in its design and coordination. TS participated in the pharmacological basis of the study. TK participated in the coordination of this study and instructed the collaborators of this manuscript.

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