Table 1　ESD（透明フード使用）と粘膜把持鉗子用チャンネル付き透明フードを使用した食道 ESD の比較（動物実験による検討）．

	A 群：ESD（透明フード）n＝6	B 群：ESD（粘膜把持鉗子用チャンネル付き透明フード）　n＝12	有意差（Student t 検定）
施行時間（分）	116.17±16.00 平均値±標準偏差	79.00±11.39 平均値±標準偏差	p＜0.05 有意差あり
止血操作（回）	5.33±1.51	2.67±1.07	p＜0.05
止血時間（秒）	67.50±9.35	34.41±14.57	p＜0.05
剝離時ブラインド率（％）	39.33±6.65	0.00±0.00	p＜0.05
穿孔（回）	1（pin hole）	0	

Table 2　透明フード使用（1点固定）と粘膜把持鉗子用チャンネル付き透明フード使用（2点固定）した食道 ESD における呼吸性変動および抑制率の比較（動物実験による検討）．

	A 群：ESD（透明フード）n＝6	B 群：ESD（粘膜把持鉗子用チャンネル付き透明フード）　n＝12	有意差（A 群 1 点固定変動 vs. B 群 2 点固定変動）（Student t 検定）
固定前変動（mm）	6.17±0.75	5.83±0.89	
1 点固定変動（mm）	1.83±0.41	1.98±0.57	
変動抑制率（％）	70.4±4.34	66.29±6.66	
有意差（固定前 vs. 1 点）（Student t 検定）	p＜0.05 有意差あり	p＜0.05 有意差あり	
2 点固定変動（mm）		0.43±0.25	p＜0.05
変動抑制率（％）		92.78±3.61	有意差あり
有意差（固定前 vs. 2 点）（Student t 検定）		p＜0.05 有意差あり	

右側の有意差検定は，A 群 1 点固定による変動（A 群網掛け部）と B 群 2 点固定による変動（B 群網掛け部）との間のものである．

筋層と平行に軽く当てて通電するもので，組織をフックすることなく容易に剝離可能である．連続して剝離する場合には，アームカットを施行した．出血や処理すべき血管は直視下に観察し，フックナイフ（フォースト 40w）または止血鉗子（ソフト凝固 60w）で出血点や血管を処理した．二群間の比較検討は ESD 施行時間，止血操作回数，止血時間，呼吸性変動抑制率および粘膜剝離時直視下に剝離部を捉えられない時間の割合（ブラインド率）で比較検討し，統計学的有意差検定として Student t 検定を使用した．呼吸性変動抑制率は，ゴム風船で作成したメジャーを挿入し，フード接着（1点固定）およびフード接着と粘膜把持（2点固定）する前の食道壁呼気時の目盛と吸気時の目盛の差と剝離時（A 群では粘膜へのフード接着のみ，B 群ではフード接着のみと把持とフード接着による2点固定）の食道壁呼気時の目盛と吸気時の目盛の差を測定することによって算出した．

また，呼吸性変動抑制に対する有意差検定は，A 群の症例ではフードのみと B 群の症例ではフード（把持なし）およびフードと把持による二点固定時と，おのおの固定前変動との間で行なった．さらに，A 群 1 点固定による変動と B 群 2 点固定による変動との間でも，二群間の有意差検定を行なった．

III　結　果

　動物実験：雑犬の食道粘膜下層の結合組織はヒトとは異なり密であるため，ヒトほど容易に lifting しません．このため，局注・切開・剝離ともに時間がかかることになりフードをもぐらせる剝離に時間がかかり，粘膜翻転・出血点確認・剝離粘膜のカウンタートラクションは，Table 1, 2 で示すように A 群は不十分であり，穿孔が 1 例に見られ，止血操作の遅れにつながった．一方，B 群では，局注・切開に関しては A 群と同様に時間はか

かるものの，８例とも剥離粘膜のカウンタートラクションは良好であり，穿孔は見られず出血点は全例確認でき止血操作の遅れもなかった．また，フードの粘膜接着により一点のみで固定するA群では全例，呼吸性変動による食道の動きを70%程しか抑えられず，食道壁の動き（呼吸）に合わせて処置具の出し入れを微調整する必要が生じたが，これと比べて粘膜把持とフードの接着の2点で固定を行うB群では，2点間の粘膜下層剥離部に対し，呼吸性変動を90%強抑えることができ，処置部の動きを最小に抑えることで粘膜剥離を安全に施行することができた．ESD施行時間は，A群で平均2時間であったが，B群では平均80分（最短で60分，最長でも88分）であった．両群の比較検討で，B群では切開・剥離に要した施行時間は短く，止血回数の少なさおよび止血鉗子を使用した止血時間の短さ，食道壁の呼吸性変動抑制率は大きく，全て両群間に有意差を認めた．また，剥離操作を通して剥離する部位を直視下に捉えられない割合（ブラインド率）は0%でありこれも有意差を認めた．病理標本の所見では，両群ともに粘膜下層での十分な切除となっていた．心拍動の影響は食道の管腔内側に上下する動きであり，定量しての比較が困難だったため検討しなかったが，鉗子による把持とフードの接着による2点固定の間の処置部は呼吸性変動と同等に，ほぼ完全に動きを抑えることができた．

IV　考　　按

われわれは動物実験でESDの訓練を繰り返した後，二年前よりESDを直径20 mm以上の早期胃癌病変に施行してきた．この実験と臨床でのESD施行症例を検討した結果，現在行なわれているESDの改善点は，手技全体を通して剥離面を定常的かつ十分に観察できない，剥離する粘膜下層組織に十分なカウンタートラクションをかけられない，処置具と切開・剥離部の距離を保持することができない点であることが判明した．これらの点を克服し，安全で確実，さらに従来法より短時間で施行可能なESD手技確立のため，粘膜把持鉗子用チャンネル付き透明フードを試作し，院内の倫理委員会の承認を得て，2005年12月より早期胃癌症例に施行し良好な成績を得て，これを報告してきた．今回はさらに動物実験を重ね，食

道のESDに対しても本法が非常に有用な手技であることが判明したため，実験結果とともに報告することとした．

現在までいろいろな食道のESD処置具・補助具・切除法が開発[5)~8)]されてきたが，前記の改善点すべてを満足するには至っていない．視野を確保し，出血点を確認，カウンタートラクションをかけて粘膜剥離を進めるため，先端フードが用いられ，切開直後の剥離面に入り込むにはSTフード（Small caliber-tip Transparent Hood）[6)]が使用されるものの，どちらも剥離部に押し付けて処置をするために視野が狭くなるという問題が残る．これに反して，われわれの粘膜把持鉗子用チャンネル付き透明フードは，通常の内視鏡に装着するだけで，粘膜切開直後から把持鉗子で粘膜剥離面を広げて十分な視野を確保することが可能であり，出血点や予防的に凝固する血管の観察を容易に行える．また，本法では把持した粘膜の下層どこからでも剥離を始められ，フードを直接押し付けてのカウンタートラクションだけでなく，鉗子で剥離粘膜の手前側を把持して後方に押す（把持鉗子を出す）だけで粘膜は翻転し十分な視野と剥離部との一定の距離が得られ，これから剥離する粘膜下組織に充分なカウンタートラクションがかけられることから，安全・容易に剥離が可能である．さらに食道では特に重要な点であるが，小山らが報告[8)]しているようにフックナイフは呼吸性変動に合わせて使用する必要があった．これに対して本法は，剥離粘膜を鉗子で把持して先端フード縁を粘膜に接着させる二点固定することによって，剥離に用いる処置具と剥離部位との距離を一定にして呼吸性変動および拍動による食道壁の動きを抑制するという利点も見られる．

今回，実験で用いた粘膜把持鉗子用チャンネル付き透明フードは，シリコン性の斜型アスピレーションムコゼクター（クリエートメディック）の先端部を切ったものを使用している．本デバイスは，Q260J（OLYMPUS）に装着すると，デバイスの鉗子用チャンネル（把持鉗子）とQ260Jの鉗子口（処置具）およびQ260Jのウオータージェットを使用することが可能となり，ESDで必要な機能が満たされることになる．

また，われわれが用いたフックナイフのアームの背側を固有筋層と平行に滑らせるアームカット

による安全な連続剥離を可能としたのも粘膜把持鉗子用チャンネル付き透明フードを使用したからである．粘膜を把持しているために剥離距離（フックナイフの動き）に制限がかかり，ナイフが滑り誤って切りすぎることが無いためである．

　本手技は把持鉗子 10-11 時，フードによる接着 6 時の 2 点で保持し，この 2 点間の常時カウンタートラクションをかけられた粘膜下層を 8 時方向から出すフックナイフで剥離していくというものであり，常にこの位置をキープすることを原則とする．また，スコープのシャフトを捻ることで接着した 6 時の粘膜と把持部の位置は保たれ，その中間に位置する粘膜下層にフックナイフが当たることになる．また，把持した粘膜はいつまでも同じ位置を把持するのではなく，中央把持の剥離のみではなく，右側辺縁を剥離する時は右側寄りに把持し直し，左側辺縁が剥離しづらければ左側寄りを把持して剥離を進め，大きな剥離粘膜が邪魔になるときは辺縁ではなく剥離された粘膜の剥離面を 3 時－9 時に向けた把持鉗子で把持することで常時同じ調子で剥離が行なえ，スコープ操作の制限を解除することができることになる.つまり，剥離してゆく部位に応じて把持する部位を変えることを心がけることが重要となる．

　今回の実験から，ESD 手技を安全・確実・短時間で施行でき得る粘膜把持鉗子用チャンネル付き透明フードは食道の ESD における有用な補助具であることが明らかとなった．われわれは，さらなる実験と症例を重ねて安全で確実な ESD 手技の確立を目指すつもりである．

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UTILITY OF AN ESD PROCEDURE OF ESOPHAGUS USING ASSISTIVE DEVICE (TRANSPARENT HOOD WITH MUCOSA GRIPPING CHANNEL ATTACHED) (AN EXAMINATION OF ANIMAL STUDIES)

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In pursuit of shortoning of procedure time and a safty and convenient improvement in endoscopic submucosal dissection (ESD) of esophagus, we experimentally produced a transparent hood with a mucosa gripping channel attached. An examination of animal studies using mongrel dogs was done. We compared a group to enforce ESD which used this device with a group to enforce conventional ESD which used only a transparent hood and reviewed it.

The use of this assistive device has the following advantages. ① By lifting the separated mucosa, then reversing and pressing it backword, the mucosa-stripped plane can be observed under direct vision. This procedure not only makes hemostasis and blood vessel processing easy, but also perforation difficult to be occurred. ② Reliable counter-traction can be applied to the submucosal tissue of the stripped plane, and separation time could be shortened. ③ Especially this method of gripping the excised mucosa and attaching the hood to the opening side of the excised reduces the effects of respiration and pulsation, keeps the distance of the separated part and instrument constant and enables safe separation procedure of esophagus.

Its utility was confirmed in animal experiments, and it can be expected similar utility in clinical application.

ORIGINAL ARTICLE

A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer

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Abstract
Purpose The aim of this study was to assess the efficacy and toxicity of weekly irinotecan in patients with metastatic pancreatic cancer.
Patients and methods Patients with histologically proven pancreatic adenocarcinoma, at least one bidimensionally measurable metastatic lesion, and no prior chemotherapy were selected. Irinotecan at a dose of $100 \, mg/m^2$ was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. Pharmacokinetics was examined on day 1 of the first cycle of treatment.
Results Thirty-seven of 40 enrolled patients were assessable for efficacy and toxicity. A partial response was obtained in 10 patients, giving an overall response rate of 27.0% (95% confidence interval 13.8–44.1%). The median overall survival was 7.3 months with a 1-year survival rate of 29.5%. Although toxicities were generally tolerated, one patient died of disseminated intravascular coagulation syndrome induced by neutropenia with watery diarrhea. Pharmacokinetic study showed that patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.
Conclusion Single-agent irinotecan has significant efficacy for metastatic pancreatic cancer. The toxicity with this schedule appears manageable, though it must be monitored carefully.

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Introduction

Pancreatic cancer is a highly aggressive disease, with approximately 21,000 deaths annually in Japan [7]. While surgery remains the only potential curative option for this disease, the vast majority of patients unfortunately present with advanced, unresectable disease. Although it has been demonstrated that gemcitabine is

an effective tool for palliation of symptoms and prolonging survival in patients with advanced pancreatic cancer [2], single-agent gemcitabine has shown limited benefit, with objective response rates of less than 15% and a median overall survival of around 4–6 months [2, 4, 5]. Therefore, there is a clear need to identify a new effective chemotherapeutic regimen for pancreatic cancer.

Irinotecan is a water-soluble semisynthetic derivative of camptothecin, a plant alkaloid obtained from the *Camptotheca acuminata* tree. Irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), bind to topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing double-stranded DNA breaks and consequent tumor cell death. Irinotecan is internationally approved for use in metastatic colorectal cancer, and has broad activity against other malignancies including lung cancer [6, 9, 15, 16]. Although several studies of single-agent irinotecan or irinotecan-based chemotherapy against pancreatic cancer have been reported [11, 12, 14, 18, 22], the role of irinotecan in the treatment of patients with pancreatic cancer remains unclear yet. Because there are few effective agents for pancreatic cancer to date, it is important to determine the clinical efficacy of irinotecan for this disease. We, therefore, conducted an open-label, multicenter, single-arm phase II study to evaluate the efficacy and toxicity of single-agent irinotecan in patients with pancreatic cancer. In the current study, we adopted weekly administration of irinotecan because safety of this schedule has been confirmed in other cancers in Japan [6, 9, 16]. Since patients with pancreatic cancer tend to suffer various tumor-related complications such as obstructive jaundice and impaired liver function, pharmacokinetic study was also performed.

Patients and methods

Patient selection

Patients were entered into the study if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; at least one bidimensionally measurable metastatic lesion; no history of prior chemotherapy or radiotherapy; age 20–74 years; Karnofsky performance status (KPS) ≥ 50 points; estimated life expectancy ≥ 2 months; adequate bone marrow function (WBC count $< 12{,}000$ per mm^3, neutrophil count $\geq 2{,}000$ per mm^3, platelet count $\geq 100{,}000$ per mm^3, and hemoglobin level ≥ 10.0 g/dl), adequate renal function (serum creatinine and blood urea nitrogen level $\leq$ the institu-

tional upper limit of normal), and adequate liver function (serum total bilirubin level ≤ 2.0 mg/dl, serum transaminases levels ≤ 2.5 times the institutional upper limit of normal); and written informed consent. Patients were excluded if there was a history of severe drug hypersensitivity; serious complications; central nervous system metastases; other concomitant malignant disease; marked pleural or peritoneal effusion; and watery diarrhea. Pregnant or lactating women were also excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the institutional review board of each participating center, and conducted in accordance with Good clinical practice guideline in Japan.

Treatment plan

This study was an open-label, multicenter, single-arm phase II study. Irinotecan was supplied by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsha Co., Ltd. (Tokyo, Japan). Irinotecan at a dose of 100 mg/m^2 was administered intravenously for 90 min on days 1, 8, and 15 every 4 weeks until the occurrence of disease progression, unacceptable toxicity, or the patient's refusal to continue. Prophylactic administration of antiemetic agents was allowed at the investigator's discretion. Physical examination, complete blood cell counts, biochemistry tests, and urinalysis were assessed weekly during treatments. If patients experienced neutropenia of $< 1{,}500$ per mm^3, thrombocytopenia of $< 100{,}000$ per mm^3, fever ($\geq 38°C$) with suspected infection, grade ≥ 1 or watery diarrhea, or $\geq$ grade 3 non-hematological toxicities other than nausea, vomiting and anorexia, irinotecan administration was omitted on that day and postponed to the next scheduled treatment day. If patients experienced neutropenia of < 500 per mm^3, thrombocytopenia of $< 50{,}000$ per mm^3, fever ($\geq 38°C$) with suspected infection, or grade ≥ 2 or watery diarrhea at any time, the irinotecan dose of the subsequent cycle was reduced by 20 mg/m^2. Patients went off study if they required more than two dose reductions. If the next cycle could not start within 4 weeks from the scheduled day, the patient was withdrawn from the study. The toxicity of irinotecan therapy was evaluated according to the National Cancer Institute Common Toxicity criteria version 2.0.

Evaluation

Objective tumor response was evaluated every 4 weeks according to the Japan Society for Cancer Therapy (JSCT) criteria [8], which is similar to the WHO crite-

ria. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks. A partial response (PR) was defined as a ≥ 50% reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. No change (NC) was defined as a < 50% reduction or a < 25% increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions. Progressive disease (PD) was defined as a ≥ 25% increase or the appearance of new lesions. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately [1]. Objective tumor response was secondarily assessed according to the response evaluation criteria in solid tumors (RECIST criteria) [20] among patients with at least one measurable metastatic lesion whose longest diameter measured by CT is no less than double the slice thickness. An external review committee confirmed objective responses and toxicities.

Clinical benefit was evaluated on the basis of established criteria [13]. Each patient was classified as a clinical benefit responder or non-responder on the basis of the change in two parameters of clinical benefit (pain and KPS). In the current study, the body weight was not used to evaluate clinical benefit response because the body weight of patients with pancreatic cancer sometimes increases due to not only improvement of their condition but also retention of malignant ascites. A positive response for pain was defined as an improved pain intensity of ≥ 50% from baseline for ≥ 4 weeks, or a decreased morphine consumption of ≥ 50% from baseline for ≥ 4 weeks. A positive response for KPS was defined as an improved KPS of ≥ 20 points from baseline for ≥ 4 weeks. To be classified as a clinical benefit responder, a patient had to achieve a positive response in at least one parameter (pain or KPS) without being negative for the other, sustained for ≥ 4 weeks.

Pharmacokinetics

To investigate the impact of biliary drainage on pharmacokinetics of irinotecan, we planned to recruit five patients each with and without biliary drainage. Heparinized blood samples (5 ml) for the pharmacokinetic study were obtained before infusion of irinotecan, at the end of the 90 min infusion, and 0.5, 1, 2, 4, 6, 8, 24 h after the completion of infusion on day 1 of the first cycle. Blood samples were immediately centrifuged at 3,000 rpm for 10 min to remove plasma and stored in polyethylene tubes at −20°C until analysis. Quantitative analysis of total irinotecan and its metabolites, SN-38, SN-38 glucuronide, and 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC) was performed by methods previously described [17, 19].

Statistical analysis

The primary goal was to evaluate the response rate (CR and PR) of irinotecan. The 95% confidence interval for response rate was calculated based on the binomial distribution. The response duration was defined as the interval from the first documentation of response to the first documentation of tumor progression. The time to progression (TTP) was calculated from the date of study enrollment to the first documentation of tumor progression; and overall survival was calculated from the date of study enrollment to the date of death or the last follow-up with censored value. Median overall survival and the median TTP were estimated by the Kaplan–Meier method and 95% confidence interval were estimated based on the Greenwood's formula. A total of 35 patients were planned to be enrolled based on the assumptions that the expected response rate of irinotecan was 15% and the threshold rate was 5%. A two-stage design was used in this study. The interim analysis was planned when 15 patients were enrolled in the first stage of the study. If the upper limit of the 90% confidence interval (one-sided) did not exceed the expected rate of 15% (no objective response in the 15 patients), irinotecan was judged to be ineffective and the study was ended. If an objective response was observed in any of the first 15 patients, additional 20 patients were enrolled in the second stage of accrual to estimate the response rate. If 6 or more out of 35 patients achieved objective response, the lower limit of the 95% confidence interval (two-sided) exceeds the threshold rate of 5%, and then the agent would be considered to be active for metastatic pancreatic cancer.

Results

Patients

Forty patients were enrolled in the study by 7 institutions between August 2001 and November 2002. Of the 40 patients, 3 patients who did not receive irinotecan because of rapid tumor progression or protocol violation were excluded from analysis. Patient characteristics of the remaining 37 patients are listed in Table 1.

All 37 patients had metastatic disease and had a good KPS of $\geq$ 80. Morphine was prescribed for 10 patients due to abdominal or back pain and 14 patients were assessable for clinical benefit response. Seven patients had recurrent disease after pancreatic resection. Two patients underwent percutaneous transhepatic biliary drainage for obstructive jaundice prior to study enrollment.

Treatments

Data were collected through May 4, 2004, providing 18 months of survival follow-up from the time accrual ended. Thirty-seven patients were given a total of 108 cycles of therapy, with a median of 2 cycles each (range 1–10). The administration of irinotecan on day 8 and day 15 was performed in 87 (80.6%) and 76 (70.4%) of 108 cycles, respectively. Dose reduction was required in 13 patients (35.1%), mainly due to diarrhea and fever with suspected infection. At the time of analysis, all patients had discontinued the study because of disease progression ($n = 28$), toxicity ($n = 5$), treatment-related death ($n = 1$), and withdrawal of consent due to other reasons ($n = 3$). After discontinuation of irinotecan, 26 patients received gemcitabine monotherapy or gemcitabine-based combination therapy; one patient was treated with S-1, and remaining 10 patients underwent only supportive care. Among 27 patients treated with second-line chemotherapy, 2 patients who received gemcitabine monotherapy achieved a PR.

Efficacy

Of 37 patients, 10 patients achieved a PR according to the JSCT criteria (Table 2). The overall response rate was therefore 27.0% (95% confidence interval 13.8–44.1%) with median response duration of 4.1 months (range 0.9–7.1 months). The median TTP was 2.1 months (range 0.7–9.5 months), and the median overall survival of 7.3 months (range 0.7–25.9 months) with a 1-year survival rate of 29.5% (Fig. 1). Of 29 patients assessable for RECIST criteria, a PR was seen in 8 patients (27.6%), stable disease in 6 patients (20.7%), and PD in 12 patients (41.4%). With regard to clinical benefit, 2 of 14 evaluable patients had pain relief and were classified as a responder (Table 3).
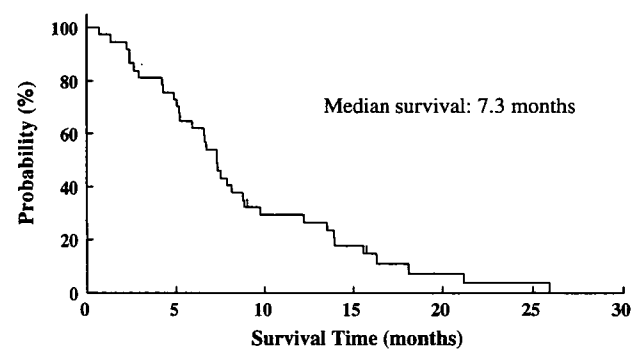

Fig. 1 Overall survival curve of all 37 patients

Table 1 Patient characteristics ($n = 37$)

Characteristics		No. of patients (%)
Gender		
Male		25 (67.6)
Female		12 (32.4)
Median age, years (range)	59 (41–74)	
Karnofsky performance status, point		
100		8 (21.6)
90		25 (67.6)
80		4 (10.8)
Median body surface area (m²) (range)	1.55 (1.31–1.85)	
History of surgical resection		7 (18.9)
PTBD		2 (5.4)
Sites of metastasis		
Liver		33 (89.2)
Lymph nodes		17 (45.9)
Lung		8 (21.6)
Others		3 (8.1)

PTBD percutaneous transhepatic biliary drainage

Table 2 Efficacy results

	No. ($N = 37$)	%
Tumor response		
Partial response	10	27.0
No change	7	18.9
Progressive disease	17	45.9
Not evaluable	3	8.1
Time to progression (months)		
Median	2.1	
Range	0.7–9.5	
Overall survival (months)		
Median	7.3	
Range	0.7–25.9	
1-year survival rate		29.5

Table 3 Clinical benefit response ($n = 14$)

		Karnofsky performance status		
		Improved	Stable	Worse
Pain	Improved	0	2	0
	Stable	0	6	1
	Worse	0	5	0

Toxicity

All 37 patients were assessable for toxicity. The major toxicities observed during the study are summarized in Table 4. The most common toxicities were hematological toxicity and gastrointestinal toxicity. Grade 3 or 4 neutropenia occurred in 10 patients (27.0%) and 5 patients received granulocyte-colony stimulating factors. The neutrophil count nadir typically occurred on day 21, and recovered to baseline values by day 28. Although nausea, vomiting, and anorexia were observed frequently, most of these toxicities recovered spontaneously or with adequate supportive treatment. Grade 3 diarrhea occurred in four patients and they were treated with loperamide. Most diarrheas appeared during the first cycle of treatment: the median time to the worst day of diarrhea was 13 days from the initiation of a cycle of therapy. Though the toxicities were mild to moderate in severity and short in duration, one patient died at day 21 of the first cycle of treatment because of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and watery diarrhea due to irinotecan. The patient, a 58-year old woman with pretreatment KPS of 100, developed grade 4 neutropenia on day 12 complicated by fever (38.8°C) and grade 3 diarrhea that evolved to fatal shock despite aggressive medical management.

Table 4 Treatment-related adverse events ($n = 37$): worst grade reported during treatment period

Toxicity	Grade				Grade 1–4 (%)	Grade 3–4 (%)
	1	2	3	4		
Hematologic						
Leukopenia	15	6	8	1	81.1	24.3
Neutropenia	5	11	8	2	70.3	27.0
Anemia	0	14	3	0	45.9	8.1
Thrombocytopenia	1	1	1	1	10.8	5.4
Non-hematologic						
Nausea	7	12	15	–	91.9	40.5
Vomiting	7	14	5	0	70.3	13.5
Diarrhea	15	8	4	0	73.0	10.8
Constipation	1	8	2	0	29.7	5.4
Anorexia	4	7	14	1	70.3	40.5
Stomatitis	2	0	0	0	5.4	0
Rash	1	0	0	0	2.7	0
Alopecia	24	1	–	–	67.6	–
Fatigue	3	8	1	1	35.1	5.4
Fever	3	1	0	0	10.8	0
Infection	2	1	4	1	21.6	13.5
Total bilirubin	4	1	1	0	16.2	2.7
AST	5	5	2	0	32.4	5.4
ALT	4	4	3	0	29.7	8.1
Hyponatremia	6	0	3	0	24.3	8.1
Creatinine	0	0	2	0	5.4	5.4

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Pharmacokinetics

A pharmacokinetic analysis was performed in five patients without biliary drainage and in two patients who underwent percutaneous transhepatic biliary drainage (Planned five patients could not be enrolled in drainage group because only two patients had biliary drainage in the current study). Table 5 and Fig. 2 show the pharmacokinetic parameters for irinotecan and its three major metabolites in patients with and without biliary drainage. Although it was difficult to assess the influence of biliary drainage in this study because of the small number of subjects analyzed, patients with biliary drainage seemed to have higher area under the concentration versus time curve for irinotecan and its metabolites compared with patients without biliary drainage.

Discussion

The prognosis of the patients with pancreatic cancer remains poor even after a randomized study demonstrated survival advantage of gemcitabine against advanced pancreatic cancer, indicating necessity of new effective agents or combination regimens for this dismal disease. Irinotecan, which has a quite different mechanism from gemcitabine, has been considered one of the attractive agents for pancreatic cancer, since this agent has demonstrated substantial activity in various types of malignant tumor [6, 9, 15, 16]. The current multicenter phase II study was, therefore, conducted to evaluate the efficacy and toxicity of single-agent irinotecan in patients with metastatic pancreatic cancer.

In this study, we found that weekly irinotecan demonstrated a good overall response rate of 27.0% in 37 patients with metastatic pancreatic cancer. In addition, a relatively long median overall survival of 7.3 months was shown, though all patients in our study had metastatic disease. As to clinical benefit response, 2 of 14 patients achieved clinical benefit response. These results indicate that irinotecan has a substantial antitumor effect on pancreatic cancer.

The major toxicities of irinotecan that were seen in the study were myelosuppression and gastrointestinal toxicities, similar to the previous observation of irinotecan monotherapy in other cancers [6, 9, 16]. Most toxicity was mild to moderate, and manageable with conservative treatment. However, one patient died of disseminated intravascular coagulation syndrome and multiple organ failure induced by neutropenia and diarrhea. Pretreatment condition of this patient was good (KPS = 100), and it was difficult to predict these

Fig. 2 Area under the concentration versus time curve for irinotecan and metabolites in patients with biliary drainage (A, $n = 2$) and without drainage (B, $n = 5$). The values are expressed as the mean ± SD
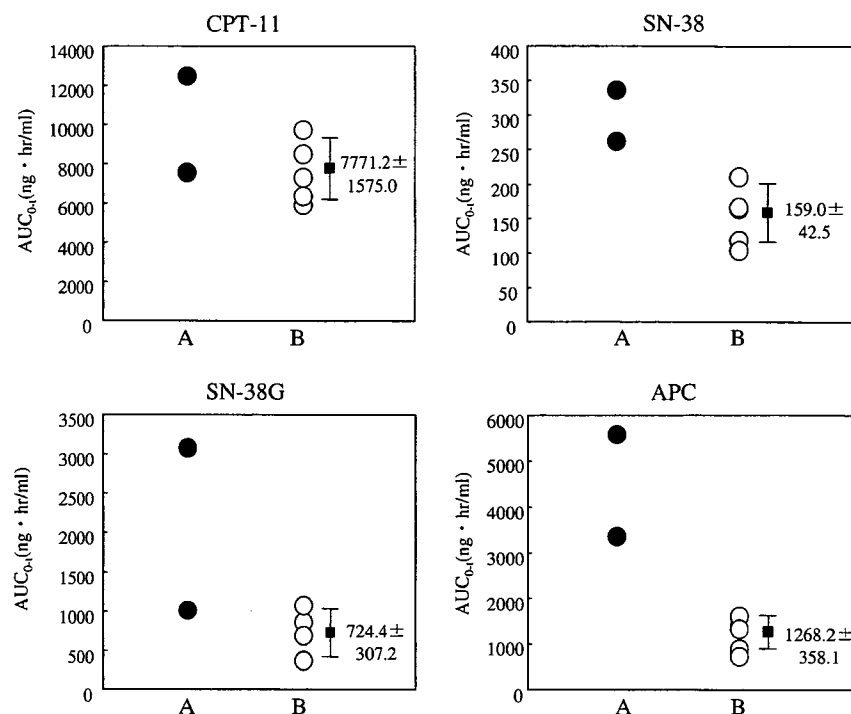

Table 5 Pharmacokinetic parameters after single administration of irinotecan at a dose of 100 mg/m^2 ($n = 7$)

		C_{max} (ng/ml)	T_{max} (h)	$T_{1/2}$ (h)	AUC$_{0-t}$ (ngh/ml)	CL (l/h m^2)
Irinotecan	A	1,188.5, 1,997.6	1.6, 1.5	7.8, 8.2	7,762, 12,692	11.8, 7.1
	B	1,701.0 ± 348.3	1.5 ± 0.1	7.7 ± 0.9	7,771.2 ± 1,575.0	12.4 ± 2.5
SN-38	A	25.5, 26.2	2.1, 1.5	14.7, 9.9	268, 342	–
	B	17.5 ± 3.8	2.3 ± 0.8	30.2 ± 27.6	159.0 ± 42.5	
SN-38G	A	81.3, 207.2	3.6, 2.0	10.8, 12.5	1,063, 3,130	–
	B	78.8 ± 34.1	2.2 ± 0.2	21.6 ± 13.2	724.4 ± 307.2	
APC	A	309.2, 359.3	2.6, 5.5	7.0, 9.5	3,441, 5,673	–
	B	116.6 ± 39.7	3.0 ± 0.6	8.8 ± 0.7	1,268.2 ± 358.1	

A Patients with biliary drainage $n = 2$

B Patients without biliary drainage (parameters are represented as the mean ± SD) $n = 5$

episodes before onset. Although our study indicated that weekly irinotecan administration would be tolerable in patients with metastatic pancreatic cancer, careful observation is required during the treatment period, since pancreatic cancer patients tend to suffer various tumor-related complications and easily take a turn to the worse because of tumor progression.

There are two studies of single-agent irinotecan that assessed efficacy and toxicity against pancreatic cancer [14, 22]. Sakata et al. [14] studied irinotecan at a dose of 100 or 150 mg/m^2 administered weekly or bi-weekly to previously treated or untreated patients with pancreatic cancer in Japan. Although 57 of 61 enrolled patients were assessable, only 4 patients (7.0%) showed a PR. This study included 28 patients (49.1%) with poor performance status of 2–3 and 22 patients (38.6%) with prior chemotherapy, and no patient

showed a PR in these patients with poor performance status or prior chemotherapy. Wagener et al. [22] demonstrated that irinotecan at a dose of 350 mg/m^2 administered every 3 weeks to chemo-naïve pancreatic cancer patients with performance status of ≤ 2, achieved a PR in 3 of 32 assessable patients (9.4%) with an median overall survival of 5.2 months. Although precise reason for the discrepant response rates between our study and the other two studies is unclear, patient background may be one possible explanation because only chemo-naïve patients with good performance status were entered into our study (89.2% of our patients had good KPS of ≥ 90).

For the purpose of the improvement on response rate and prognosis, several studies of combination therapy have been conducted in patients with pancreatic cancer. With regard to irinotecan with gemcitabine, an

encouraging activity, response rates between 20.0 and 24.7% and median overall survival between 5.7 and 7 months, have been reported in two phase II studies [11, 18]. However, survival benefit of this combination therapy was not shown in a phase III study [12], in which, 360 patients were randomized to treatment with a combination of gemcitabine 1,000 mg/m² followed by irinotecan 100 mg/m² given on days 1 and 8 of a 3-week cycle versus gemcitabine monotherapy. The response rate for the combination therapy was higher at 16.1% compared with 4.4% for gemcitabine alone, but there was no difference in median overall survival (6.3 vs. 6.6 months). However, several clinical studies have recently indicated that irinotecan-based chemotherapy seemed to be an effective treatment for advanced pancreatic cancer after gemcitabine failure: irinotecan–raltitrexed combination demonstrated overall response rate of 16% (3/19) in patients with gemcitabine-pretreated pancreatic cancer [21], and Cantore et al. [3] reported that irinotecan plus oxaliplatin showed response rate of 10% (3/30) with a clinical benefit response of 20% (6/30) for patients with advanced pancreatic cancer after gemcitabine failure.

Because biliary excretion is a major elimination pathway for irinotecan and its metabolites, we investigated the impact of biliary drainage on the pharmacokinetics for this agent. Our results suggested that patients with biliary drainage tended to have higher area under the concentration versus time curve of irinotecan and metabolites compared with patients without biliary drainage. Meyerhardt et al. [10] reported that modest elevation of bilirubin (1.0–1.5 mg/dl) is associated with increased grade 3 to 4 neutropenia in patients treated with irinotecan. The fact that the two patients with biliary drainage in the current study had slight elevation of baseline serum bilirubin level (1.4 and 1.7 mg/dl) might influence pharmacokinetics for irinotecan. Although no severe hematological or non-hematologic toxicities appeared in these two patients, careful observation may be required when treating patients with biliary drainage.

In conclusion, single-agent irinotecan showed a substantial antitumor activity for patients with metastatic pancreatic cancer, rendering a 27.0% response rate. The toxicity with this schedule appears manageable, though it must be monitored carefully.

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The Role of the Outpatient Clinic in Chemotherapy for Patients with Unresectable or Recurrent Gastric Cancer

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Background: Recently, outpatient chemotherapy centers have become popular in Japan. To clarify the actual conditions of outpatient clinics, we surveyed entire clinical courses of chemotherapy in patients with unresectable or recurrent gastric cancer.

Methods: From the medical records of 64 patients with unresectable or recurrent gastric cancer with no prior chemotherapy, we obtained data on overall survival, non-hospitalized survival, the number of and reasons for attendance at the outpatient clinic and hospitalization, and medical conditions at discharge.

Results: The median follow-up time was 520 days, the median survival time was 353 days, and the median non-hospitalized survival time was 282 days. Patients attended the outpatient clinic 1917 times in total; 145 (8%) of these were unplanned visits for accidental disease, disease progression, or toxicity. Patients were hospitalized 291 times in total: 110 (38%) of hospitalizations were unplanned or emergencies because of disease progression or toxicity. Patients were discharged 290 times in total; in 56 of these discharges (19%) unresolved medical problems remained, such as toxicity, total parenteral nutrition, or symptoms related to cancer. Three patients (5%) died from treatment-related leucopenia and thrombocytopenia.

Conclusions: Patients with unresectable and recurrent gastric cancer were treated at outpatient clinics for periods up to 80% longer than the entire clinical course of chemotherapy. However, there were some unplanned or emergency hospitalizations and some patients still experienced medical problems at discharge. The role of the outpatient clinic is very important to chemotherapy for patients with unresectable or recurrent gastric cancer.

Key words: gastric cancer — chemotherapy — outpatient clinic

INTRODUCTION

Gastric cancer is one of the leading causes of death in Japan and throughout the world. Recent progress in diagnostic procedures and surgical treatment has improved the curability of gastric cancer in the resectable stages. However, the prognosis of unresectable or recurrent gastric cancer still remains poor. Randomized trials have demonstrated that fluorouracil (5-FU)-based chemotherapy can improve survival and quality of life (QOL) in patients with unresectable or recurrent gastric cancer compared with best supportive care (1).

Although several phase III trials have been conducted for patients with advanced gastric cancer in recent decades, no standard treatment has been established.

However, various novel anti-tumor agents have been developed recently, including irinotecan (CPT-11), oral pyrimidines, taxanes and molecular target agents. Many phase I and II trials have reported on the activities of these new agents, which are used either as single agents or as combination therapy. For the patient, hospitalization deteriorates daily activity, and non-hospitalized survival can thus represent one substantial improvement to QOL. Many of these new drugs, especially oral anti-tumor drugs, can be used in an outpatient setting and may therefore contribute to prolonging the non-hospitalized survival of patients with gastric cancer treated with chemotherapy. While in Japan

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most patients for chemotherapy have received in-hospital treatment, many hospitals have recently been establishing chemotherapy centers, where efforts are made to treat patients on an outpatient basis. The Japan Clinical Oncology Group (JCOG) has adopted non-hospitalized survival time as a secondary endpoint in JCOG9912 (Randomized phase III study of 5-FU continuous infusion versus CPT-11 plus cisplatin versus S-1 in advanced gastric cancer).

In gastric cancer, conditions of patients may deteriorate suddenly as a result of various complications such as peritoneal dissemination, which is usually undetectable by radiological imaging and sometimes causes bowel obstruction, hydronephrosis and obstructive jaundice. It is suggested that management of gastric cancer by chemotherapy at outpatient clinics may be more difficult than other non-digestive malignancies.

Few reports have documented the clinical course from the initiation of treatment to death in patients with gastric cancer treated with chemotherapy, and actual problems in outpatient clinics have scarcely been reported in detail. For example, it is not even known how long the non-hospitalized survival is and what kind of problems are encountered at outpatient clinics during chemotherapy and therefore we are left to conclude that the provision of chemotherapy over a full clinical course for cancer patients is still in its infancy in Japan. In this retrospective study, we surveyed the entire clinical course of patients with unresectable and recurrent gastric cancer treated with chemotherapy to investigate the actual conditions of outpatient clinics during cancer treatment, in order to improve the system in the near future.

PATIENTS AND METHODS

PATIENT SELECTION

From 199 patients with unresectable and recurrent gastric cancer receiving chemotherapy at the Shizuoka Cancer Center between September 2002 and March 2004, we selected patients who fulfilled the following eligibility criteria listed in JCOG9912: (i) histologically proven unresectable or recurrent adenocarcinoma of the stomach, except for patients whose unresectable cancer was limited to class V by cytological examination of the abdominal cavity or with no visible tumor; (ii) no prior chemotherapy; (iii) adequate oral intake without nutritional support; (iv) no severe peritoneal dissemination associated with massive ascites or remarkable findings detected by barium enema; (v) age between 20 and 75 years; (vi) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or better; (vii) no massive pleural effusion; (viii) no other active malignancies; (ix) adequate bone marrow (white blood count $3000-12\,000/\mu l$, platelets $\geq 100\,000/\mu l$), renal (creatinine: ≤ 1.5 mg/dl), and hepatic functions (aspartate aminotransferase ≤ 99 IU/l, alanine aminotransferase ≤ 99 IU/l, bilirubin ≤ 2.0 mg/dl); (x) no other serious medical complications; (xi) no

symptomatic brain metastasis; and (xii) written informed consent for chemotherapy.

TREATMENT SCHEDULE

All chemotherapy regimens were approved in clinical practice to treat patients with gastric cancer by the Clinical Practice Review Committee of the Shizuoka Cancer Center. All patients provided informed consent before chemotherapy was initiated and the chemotherapy continued until tumor progression, unacceptable toxicity, or patient's refusal to continue. For each patient, the chemotherapy regimen was selected according to the patient and physician's choice for the first-line treatment. Treatment was generally performed by the following schedule: (i) S-1 alone: S-1 (40 mg/m^2 per day, orally twice daily) on days 1–28 every 6 weeks (2,3); (ii) S-1 and cisplatin (CDDP): S-1 (40 mg/m^2 per day, orally twice daily) on days 1–21 and CDDP (70 mg/m^2, intravenously) on day 8 every 5 weeks (4); (iii) sequential methotrexate (MTX) and 5-fluorouracil (5-FU): weekly administration of MTX (100 mg/m^2, bolus) followed by 5-FU (600 mg/m^2, bolus) at 3-h intervals, calcium leucovorin (10 mg/m^2, orally or intravenously) administered six times every 6 h starting 24 h after MTX (5), (iv) CPT-11 and CDDP: CPT-11 (70 mg/m^2, intravenously) on days 1 and 15, and CDDP (80 mg/m^2, intravenously) on day 1 every 4 weeks (6); (v) 5-FU continuous infusion (5-FU c.i.): 5-FU (800 mg/m^2, continuous infusion) on days 1–5 every 4 weeks (7); (vi) weekly paclitaxel (w-PTX): weekly administration of PTX (80 mg/m^2, intravenously) for 3 weeks every 4 weeks (8); (vii) CPT-11 and mitomycin C (MMC): CPT-11 (150 mg/m^2, intravenously) and MMC (5 mg/m^2, bolus) every 2 weeks (9); (viii) 5-FU and isovorin (l-LV): weekly administration of 5-FU (600 mg/m^2, bolus) and l-LV (250 mg/m^2, 2-h infusion) for 6 weeks every 8 weeks (10); (ix) 5-FU and CDDP: 5-FU (800 mg/m^2, continuous infusion) on days 1–5 and CDDP (80 mg/m^2, intravenously) on day 1 every 4 weeks (7); (x) CDDP injected intraperitoneally (11); (xi) CPT-11 alone: CPT-11 (150 mg/m^2, intravenously) every 2 weeks (12,13); (xii) CDDP and etoposide (VP-16): CDDP (80 mg/m^2, intravenously) on day 1 and VP-16 (100 mg/m^2, intravenously) on day 1 every 3 weeks (14); (xiii) hepatic arterial infusion (HAI): 5-fluorouracil (333 mg/m^2) each week, epirubicin (30 mg/m^2) once every 4 weeks and mitomycin-C (2.7 mg/m^2) once every 2 weeks administered by HAI (15); (xiv) MMC alone: weekly administration of MMC (5 mg/m^2, bolus). Dose and schedule were modified according to each patient's medical condition and any toxicities observed in the previous courses.

EVALUATION AND STATISTICAL ANALYSIS

The overall survival time was calculated from the date of the first administration of chemotherapy of the first-line treatment to the date of death by any causes, or to the last date of confirmed survival. The non-hospitalized survival time was

estimated by subtracting the period of hospitalization by any causes from the overall survival time. We checked the number of and reasons for attendance at outpatient clinics and recorded all treatments, including supportive care, performed at each attendance. We also assessed the number of times patients were hospitalized, the reasons for hospitalization and medical conditions at discharge. We accumulated early death observed within 30 days after the last administration of chemotherapy to investigate the cause of death. Survival analysis was performed using the methods of Kaplan and Meier, by adopting all deaths from any cause as events.

RESULTS

PATIENT CHARACTERISTICS

One hundred and ninety-nine patients received chemotherapy during the study period, of whom 135 patients were excluded from analysis and 64 patients fulfilled the eligibility criteria and were entered into the study. The reasons for exclusion were prior chemotherapy (70 patients), no visible tumor (13 patients), older than 76 years (13 patients), severe peritoneal dissemination (10 patients), inadequate oral intake (nine patients), other active malignancy (eight patients), serious medical complication (seven patients), PS 3 or 4 (four patients), and symptomatic brain metastasis (one patient). Table 1 shows the characteristics of the patients. The median age was 64 years (range 32–75 years); 30 patients were PS 0, 27 patients were PS 1, and seven patients were PS 2. One patient had no metastatic sites, 34 patients had one metastatic site, 22 patients had two metastatic sites, eight patients had three or more metastatic sites.

TREATMENT

Table 2 lists the chemotherapy regimens received over the entire clinical courses of the patients. The median number of regimens was two (range, 1–6), 72% of patients received second-line chemotherapy, and 39% of patients had three or more chemotherapy regimens. In 31 patients (48%), the first-line chemotherapy was started at the outpatient clinic. Oral administration of S-1 was the most frequently used in

Table 1. Patient characteristics

Age (years)		
	Median	64
	Range	(32–75)
Gender		
	Male	46
	Female	18
PS	0/1/2	30/27/7
Number of metastatic sites	0/1/2/3/4	1/34/21/6/2

PS, performance status.

first-line chemotherapy (35 patients, 55%), and 21 (33%) patients who were given CDDP-containing regimens or continuous infusion of 5-FU required hospitalization. The most frequently used forms of second-line chemotherapy were w-PTX (26 patients, 57%) and a combination of CPT-11 and CDDP (11 patients, 24%).

ATTENDANCE AT THE OUTPATIENT CLINIC

Table 3 lists the number of and reasons for attendance at the outpatient clinic. The median number of visits to outpatient clinics was 29 visits per patient (range, 0–84). The total number of visits was 1917, of which 145 (8%) were unplanned, which were caused by accidental disease (50 visits), disease progression (46 visits), toxicity (45 visits), or for prescription (four visits). Supportive care was performed in outpatient clinics at 142 visits (7%) such as hydration (88 visits), transfusion (28 visits), abdominal paracentesis (eight visits), insertion of a central venous line (seven visits), and administration of granulocyte colony-stimulating factor (two visits).

SURVIVAL AND HOSPITALIZATION

Although some patients were referred to other hospitals, we obtained the information concerning the reason and period

Table 2. Treatment

	1st line	2nd line	3rd line	≥4th line
	$n = 64$	$n = 46$	$n = 25$	$n = 10^*$
S-1	35	5	–	3
S-1/CDDP	10	1	–	–
MTX/5-FU	7	–	–	3
CPT11 + CDDP	6	11	2	–
5-FUci	5	–	–	–
Weekly PTX	1	26	12	2
CPT11 + MMC	–	3	4	–
5-FU/I-LV	–	–	2	3
5-FU + CDDP	–	–	–	1
CDDPip	–	–	2	–
CPT-11	–	1	2	–
CDDP + VP-16	–	–	–	1
Hepatic arterial infusion	–	–	1	2
MMC	–	–	–	1

*Repetition (+).
S-1, tegafur-gimeracil-oteracil-potassium; CDDP, cisplatin; MTX, methotrexate; 5-FU, 5-fluorouracil; CPT11, irinotecan; ci, continuous infusion; PTX, paclitaxel; MMC, mitomycin; I-LV, I-leucovorin; ip, intra peritoneum; VP-16, etoposide.

Table 3. Attendance to outpatient clinic and providing supportive care

	Number	Median	(Range)
Total	1917	29	(0–84)
Planned	1772	25	(0–79)
Emergent	145	2	(0–10)
Accidental disease	50		
Disease progression	46		
Side effect	· 45		
Prescription	4		
Supportive treatment	142		
Hydration	88		
Transfusion	28		
Abdominal paracentesis	8		
Insertion of CV line	7		
Exchange of drainage	5		
G-CSF	. 2		
Wound care	2		
Enema	1		
Withdrawing of urine	1		

CV, central venous; G-CSF, granulocyte colony-stimulating factor.

Figure 1. Overall survival.

of hospitalization, and the date and cause of death by making inquiries directly to these hospitals.

The median follow-up was 520 days (range, 309–871 days), and the median overall survival time was 353 days. The 1-year survival rate was 49%, while the 2-year survival rate was 26% (Fig. 1). The median non-hospitalized survival time was 282 days (range, 0–786 days) and the median total period of hospitalization for each patient was 59 days (range, 0–138 days) (Fig. 2). The median number of hospitalizations was four (range, 0–15) per patient and the median period of each hospitalization was six days (range, 1–96 days). The total number of hospitalizations was 291, of which 110 (38%) were unplanned and reasons for unplanned hospitalization were related to disease progression (85 hospitalizations), toxicity (14 hospitalizations), accidental disease (nine hospitalizations), or examination (two hospitalizations) (Table 4).

MEDICAL CONDITION AT DISCHARGE

Patients were discharged 290 times (Table 5), 56 (19%) of which were associated with an unresolved medical problem needing intensive care or follow-up to be managed at the outpatient clinic. These included toxicity (14 discharges), total parenteral nutrition (14 discharges), symptoms of cancer (17 discharges), percutaneous endoscopic gastrostomy (seven discharges), and other problems (four discharges).
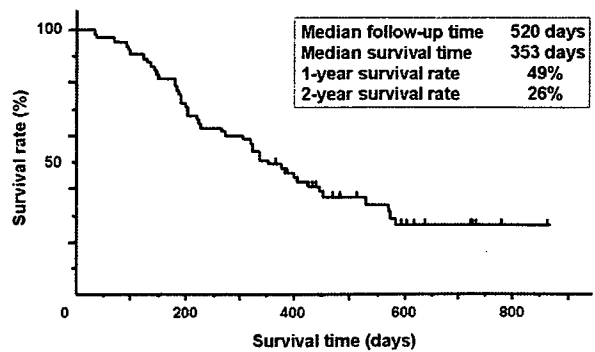
TREATMENT-RELATED DEATH

Fifteen patients (23%) died within 30 days after the last administration of chemotherapy. Of these 15 patients, three died of treatment-related death (TRD), and the other 12 early deaths within 30 days after last administration of chemotherapy occurred after confirming tumor progression. Two of three TRDs were treated at the outpatient clinic. One patient with PS 2 and massive ascites caused by peritoneal dissemination received w-PTX regimen as the second line setting. Vomiting appeared on day four after the sixth administration of chemotherapy and he entered the hospital for septic shock on the same day. Despite intensive supportive care he died on day five. Another patient with PS 1 and chronic renal failure received w-PTX regime as the third line setting. Although the only complication he had was grade 1 (NCI-CTC ver.2) nausea till day four, he entered hospital for grade 4 leucopenia on day five after the eighth administration of chemotherapy agent. While he recovered from leucopenia on day 11, grade 3 thrombocytopenia persisted. Bleeding from primary tumor occurred after confirming disease progression and he died of hypovolemic shock on day 26. The last patient died of pneumocystis carini
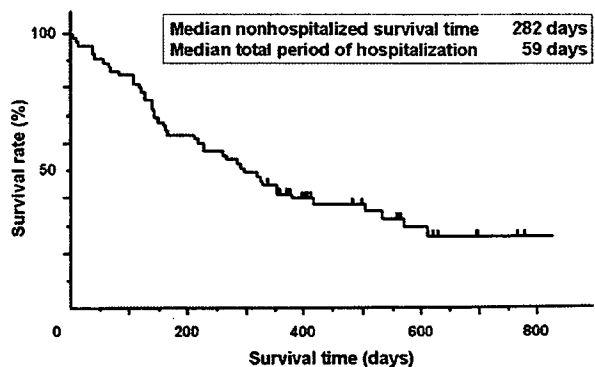

Figure 2. Non-hospitalized survival.

Table 4. Number and period of hospitalization

	Number	Median number	(Range)	Median period (days)	(Range)
Total	291	4	(0–15)	6	(1–96)
Planned	181	–		5	(1–65)
Emergent	110	–		16	(1–96)
Disease progression	85	–		21	(2–96)
Toxicity	14	–		9	(1–22)
Accidental disease	9	–		8	(2–22)
Examination	2	–		4	(3–5)

Table 5. Medical condition at discharge

	Number
Total	290
No problem	193
Death	41
Problems unresolved	56
Toxicity	14
TPN	14
Symptoms of cancer	17
PEG	7
Mental	3
PTBD	2
HOT	1
Stent in bile duct	1
Unresolved accidental disease	1

TPN, total parenteral nutrition; PEG, percutaneous endoscopic gastronomy; PTBD, percutaneous transhepatic bile duct drainage; HOT, home oxygen therapy.

pneumonia caused by grade 4 leucopenia after 1st administration of CDDP and VP-16 initiated during hospitalization.

DISCUSSION

In the recent randomized studies investigating the effects of single agent 5-FU therapy or the combination therapy of 5-FU plus CDDP, docetaxel and 5-FU plus CDDP, 5-FU and doxorubicin plus MMC or etoposide and leucovorin plus 5FU, it was reported that the median survival time was 7–9 months, the 1-year survival rate was 28–40% and 2-year survival rate was 7–18% (7,16–19).

For the single agent therapy of S-1, a novel oral derivative of 5-FU, the median survival time of 207 days, and 1- and 2-year survival rates of 36 and 14%, respectively, were reported in a Japanese phase II study (2,3). Furthermore a Japanese phase I/II study of S-1 combined with CDDP reported a median survival time of 383 days, and 1- and

2-year survival rates of 52 and 10%, respectively (4). However, a Japanese phase II study on CPT-11 combined with CDDP showed a median survival time of 322 days (6). In our study, the median survival time was 353 days, and 1- and 2-year survival rates were 49 and 26%, respectively. Although our survival data were obtained by retrospective analysis, our clinical outcomes seem to be equal or exceed those reported in previous studies.

In our study, the median non-hospitalized survival time was 282 days and median overall survival time was 352 days. We found no reports referring to non-hospitalized survival of patients with gastric cancer and it is difficult to compare our results with those of other researchers. In our hospital, we use various supportive systems to help patients remain at home and to care for patients from the initiation of chemotherapy to the terminal stage.

The incidence of TRD is 1–5% in some phase III studies (7,16). Three TRDs caused by leucopenia and thrombocytopenia occurred in our study (5%). Of two patients who were treated at the outpatient clinic, one patient entered hospital quickly after symptoms appeared. Another patient recovered from the leucopenia immediately after hospitalization so we do not consider that chemotherapy at the outpatient clinic caused delay of supportive care and that TRD might have been avoided if the patients had been treated in hospital. The number of early deaths within 30 days after the last administration of chemotherapy in our series seems high. The median number of chemotherapy regimens was two, and many patients received three or more chemotherapy regimens. Some of them were initiated despite poor medical conditions. We thus hypothesize that the risk of TRD increases according to the number of regimens received. Moreover, the indications for chemotherapy, especially in the subsequent treatment lines, should be decided more carefully to promote the safety of chemotherapy.

Most patients undergoing chemotherapy visit the hospital usually once every week or two. The median number of visits to the outpatient clinic was 29 and the median survival time was about 1 year. However, because of toxicity or disease progression, the patients' medical conditions sometimes changed between planned visits. We found that 8% of the total number of visits to the outpatient clinic were unplanned and that 7% of all visits required supportive care. We made an effort to prolong non-hospitalized survival by providing home nutrition and other supporting systems. This situation might make the incidence of unplanned attendance at the outpatient clinic look high, but we believe these are important in providing chemotherapy for patients with gastric cancer.

The incidence of unplanned or emergency hospitalization was 38% of the total number of hospitalizations. The main reason for hospitalization was worsening of patient's medical conditions caused by disease progression. Gastric cancer sometimes causes impaired oral intake, ileus, ascites, hydronephrosis and other severe complications. These serious complications can not be managed at an outpatient

clinic, and therefore the median duration of emergency hospitalization (16 days) was longer than that of planned hospitalization (five days). These data suggest the importance of establishing a system by which patients are accepted quickly for unplanned or emergency hospitalization in order to ensure safety of chemotherapy.

As mentioned above, we made an effort to prolong non-hospitalized survival by providing various support systems and 19% of the total number of discharges had associated problems such as toxicity, total parenteral nutrition at home, symptoms of cancer and percutaneous endoscopic gastrostomy. Although we helped patients adapt to these problems before discharge, our data suggest that these problems could also be managed or resolved at an outpatient clinic.

In conclusion, chemotherapy for patients with unresectable recurrent gastric cancer can be performed safely with support in hospitals. Japanese hospitals should not only establish outpatient chemotherapy centers but also a system to quickly provide emergency care during chemotherapy. We expect that the support system for providing chemotherapy safely will become more popular in Japan, and contribute to patients' QOL in the near future.

Conflict of interest statement
None declared.

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found in *H. pylori* gastritis.[10,11] With immunohisto-chemistry results with CD79a and CD138, we hypothesize that some of these crystal-laden 'histiocytes' are plasma cells that have failed to secrete immunoglobulin. Overproduction of immunoglobulins has been known to be a possible mechanism of crystal formation in CSH and has been described in plasma cell granuloma or post-transplantation plasmacytosis.[1] Although an additional or associated mechanism is uncertain at present, overproduction of immunoglobulin caused by *H. pylori* infection is a plausible aetiology. To the best of our knowledge, the present case is the second documented case of gastric CSH and the first case of localized CSH associated with polyclonal plasma cell proliferation probably caused by *H. pylori* infection.

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API2-MALT1 chimeric transcript-positive gastroduodenal MALT lymphoma with subsequent development of adenocarcinoma as a collision tumour over a clinical course of 7 years

Sir: Both gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma)[1] and gastric adenocarcinoma have a strong association with *Helicobacter pylori* infection in their pathogenesis and development,[2,3] but their collision in the stomach is rare. Furthermore, synchronous *API2-MALT1*+ MALT lymphoma and adenocarcinoma of the stomach independent of *H. pylori* infection has not been previously reported. t(11;18)(q21;q21) translocation occurs specifically in MALT lymphoma and this translocation generates a functional *API2-MALT1* fusion product which activates nuclear factor NF-κB.[4] Most cases of *API2-MALT1*+ gastric MALT lymphoma do not respond to *H. pylori* eradication.[5,6] We report a unique case of *API2-MALT1*+, *H. pylori*-negative, advanced stage, gastroduodenal MALT lymphoma in which two lesions of overt gastric adenocarcinoma developed 7 years after the initial diagnosis of MALT lymphoma.

A 63-year-old Japanese woman presented with weight loss of 14 kg over 6 months. Upper gastrointestinal endoscopy disclosed multiple erosions and oedematous mucosa throughout the stomach and a biopsy specimen revealed gastric MALT lymphoma spreading from the stomach to the duodenal bulb and second portion (Figure 1a,b). Although tissue culture and a ^{13}C urea breath test for *H. pylori* infection were negative, she received eradication therapy 2 years
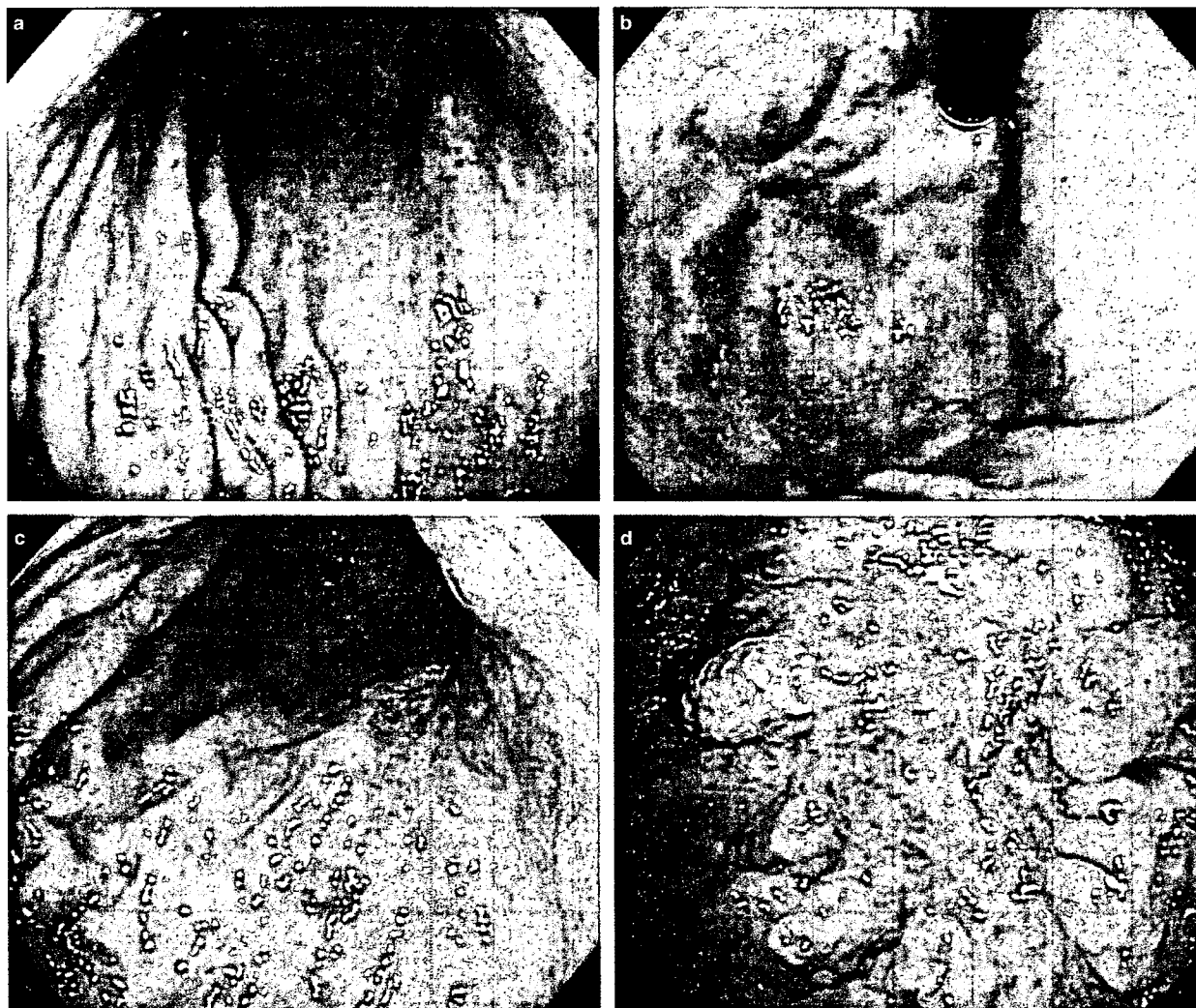
Figure 1. Upper gastrointestinal endoscopy. a,b, Upper gastrointestinal endoscopy based on the initial diagnosis shows multiple erosions and oedematous mucosa. c,d, Five years after eradication therapy, i.e. 7 years after initial diagnosis, upper gastrointestinal endoscopy reveals two lesions, Borrmann 3 gastric carcinomas, on the posterior wall of the middle gastric body (no. 1) and on the greater curvature of the upper gastric body (no. 2). Both are located within the area involving the mucosa-associated lymphoid tissue lymphoma.

after the initial diagnosis, resulting in no improvement in MALT lymphoma, and was thereafter followed without more therapy at her request. At this time, the patient was also evaluated as being at clinical stage IV with bone marrow involvement. *API2-MALT1* chimeric transcripts were detected by reverse transcriptase-polymerase chain reaction and nucleotide sequencing[7] in tissue samples obtained by biopsy and resection of the gastric MALT lymphoma. Five years after *H. pylori* eradication therapy, i.e. 7 years after the initial diagnosis, upper gastrointestinal endoscopy revealed two lesions of Borrmann 3 gastric adenocarcinoma on the posterior wall of the middle

gastric body no. (1) and the greater curvature of the upper gastric body (no. 2) (Figure 1c,d, respectively). The lesions were located within the area involved by the MALT lymphoma, thereby constituting contiguous/collision tumours. Gastrectomy was performed, but the patient eventually died of peritonitis carcinomatosa 2 months after surgery. Seven years had passed since the initial diagnosis of MALT lymphoma. No changes had been seen in the size, stage or clinical features of the MALT lymphoma over the 7-year follow-up period.

The resected stomach was opened along the lesser curvature. Figure 2 shows the macroscopic