Phase II Study of Sequential Methotrexate and 5-Fluorouracil Chemotherapy Against Peritoneally Disseminated Gastric Cancer with Malignant Ascites: a Report from the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group, JCOG 9603 Trial

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Background: The efficacy of systemic chemotherapy against peritoneal dissemination from advanced gastric cancer (AGC) remains unclear, because the peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies. In this study, we evaluated the efficacy and toxicity of sequential MTX and 5FU therapy (MF) in chemotherapy-naive patients with AGC accompanied by malignant ascites in a phase II setting.
Methods: The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 every 6 h, for a total of six times) was commenced 24 h after MTX administration.
Results: Thirty-seven chemotherapy-naive patients with AGC presenting with malignant ascites were enrolled in this trial. The median age was 60 years (range, 25–74 years) and most patients (86%) had a performance status of 0–1. In total, 355 administrations of the sequential MTX/5FU therapy were performed. Major toxicity consisted of myelosuppression and gastrointestinal toxicity. Grade 4 neutropenia occurred in 10.8% of the patients. The overall objective response rate was 5.7% (two partial responses in 35 patients; 95% confidence interval: 0.7–19.2%). However, the response rate of ascites was 35.1% (complete disappearance in three patients and apparent decrease in 10 patients; 95% confidence interval: 20.2–52.5%).
Conclusions: Sequential MTX/5FU therapy is effective against AGC with malignant ascites with acceptable toxicity and warrants further investigations in a phase III setting.

Key words: sequential MTX/5FU chemotherapy – gastric cancer, peritoneal dissemination – ascites – clinical trial

INTRODUCTION

Despite a declining incidence in many industrial countries, gastric cancer remains one of the most common malignancies globally. Although this tumor is potentially curable with surgery when diagnosed at an early stage, the prognosis for patients with unresectable or metastatic disease is very poor, with a median survival of 3–4 months when they receive the best supportive care without palliative surgery or chemotherapy (1–3). Gastric cancer can progress to systemic disease through various routes such as direct invasion or lymphatic or vascular spread. Peritoneal dissemination, i.e. peritoneal carcinomatosis, which occurs mainly as a result of direct invasion and/or lymphatic spread, is very common in advanced gastric cancer and is considered an incurable disease state (4). Peritoneal dissemination may cause serious complications, such as

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intestinal obstruction, massive ascites and hydronephrosis associated with the clinical presentation of abdominal pain and fullness, vomiting, constipation, malnutrition and renal dysfunction. From the clinical point of view, palliative management of those complications warrants special considerations and represents a therapeutic challenge in oncology (5,6). Although the major treatment option for unresectable or metastatic gastric cancer is systemic chemotherapy, this strategy has been generally believed to have little effect on peritoneal dissemination, because the drugs could not be delivered sufficiently through the peritoneum–plasma barrier to the disseminated tumor cells (7). However, the efficacy of systemic chemotherapy against peritoneal dissemination from gastric cancer remains unclear, because peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies and therefore few reports are available about the efficacy of systemic chemotherapy against peritoneal dissemination. 5-Fluorouracil (5FU) remains the mainstay for chemotherapy against gastric cancer and a variety of drugs have been tested as modulators to increase its chemotherapeutic efficacy. The modulators that have been most widely used in clinical practice against gastrointestinal tract cancers are folinic acid (leucovorin) and methotrexate (MTX) (8,9). MTX enhances 5FU cytotoxicity via DNA and/or RNA synthesis inhibition when the two drugs are administered in sequence, with 5FU administered a few hours after MTX (10,11). A meta-analysis of randomized trials of sequential MTX/5FU therapy revealed a higher response rate than for single agent bolus 5FU in colorectal cancer (12). The toxicity of these sequential MTX/5FU regimens was comparable to that of 5FU alone (i.e. vomiting, stomatitis, diarrhea and leukopenia). The sequential MTX/5FU therapy was found in phase II trials for advanced gastric cancer to have antitumor activity against advanced gastric cancer (13,14). A Japanese phase II trial of sequential MTX/5FU therapy against advanced gastric cancer demonstrated that low- and intermediate-dose MTX regimens achieved response rates of 23% (13 PRs/56 patients) and 41% (15 PRs/37 patients), respectively (15). Sequential MTX/5FU therapy is widely used as one of the standard treatment regimens for patients with unresectable or metastatic gastric cancer at present in Japan. Konishi et al. reported that sequential MTX/5FU therapy was effective in patients with peritoneal dissemination with a response rate of 23% (6/26) and that ascites disappeared in eight of 16 patients (50%) treated with this therapy (16). Those findings suggest that sequential MTX/5FU might be effective in advanced gastric cancer with peritoneal dissemination.

The objective of this study was to evaluate the efficacy and toxicity of sequential MTX/5FU chemotherapy in advanced gastric cancer with malignant ascites in order to determine whether this regimen is worthy of further investigation in a phase III trial for the treatment of patients with peritoneal dissemination from advanced gastric cancer. The primary endpoints planned for this study were tumor response rate and response rate in ascites. Secondary endpoints were overall survival and toxicity. To our knowledge, there has been no prior study that evaluated the efficacy and toxicity of systemic chemotherapy in a phase II setting in patients with advanced gastric cancer who have peritoneal dissemination with malignant ascites.

SUBJECTS AND METHODS

ELIGIBILITY

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) histologically confirmed gastric cancer; (2) unresectable or recurrent disease; (3) peritoneal dissemination with cytologically confirmed malignant ascites evaluable by CT scan or ultrasonography; (4) measurable or evaluable disease; (5) age 20–75 years; (6) performance status (PS) ≤2 on Eastern Cooperative Oncology Group (ECOG) scale; (7) no prior chemotherapy with the exception of one adjuvant chemotherapy; (8) adequate bone marrow function (WBC ≥4000/mm^3 and platelets ≥100 000/mm^3) (9) adequate liver function (serum bilirubin level ≤2.0 mg/dl and serum transaminase level ≤2.5-fold the upper limit of normal; (10) adequate renal function (serum creatinine and blood urea nitrogen within the upper limit of normal; (11) serum albumin ≥2.6 g/dl; (12) normal ECG; (13) currently hospitalized; (14) life expectancy at least 8 weeks; (15) written informed consent. Patients with active bleeding from the gastrointestinal tract, other active synchronous carcinoma, central nerve metastasis or concurrent uncontrolled medical illness and pregnant or lactating women were excluded. Patients with massive ascites that required drainage for the relief of symptoms were also excluded. The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center.

TREATMENT PLAN

The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 orally or i.v. every 6 h, six times) was commenced 24 h after MTX administration. To prevent toxicity from MTX, acetazolamide (250 mg) was given intravenously immediately after the infusion of MTX and sodium bicarbonate (33.3 mequiv.) added to 500 ml of electrolyte solution was administered by drip infusion for urine alkalinization during the 3 h interval between the administration of MTX and 5FU. The plasma level of MTX was monitored 24 h after MTX administration and leucovorin rescue at 10 mg/m^2 was administered every 6 h until the plasma level of MTX was $<1 \times 10^{-6}$ mol/l. At the time of each administration, patients were required to fulfill the following criteria: leukocyte count ≥3000/ mm^3; platelet count ≥75 000/ mm^3; adequate liver and renal function as eligibility criteria; PS 0–2; and absence of toxicity grade 2 or greater. The treatment was repeated unless disease progression or severe toxicity was observed. The treatment was terminated when the ascites did

Table 1. Patients' characteristics

Characteristic	Total ($n = 37$)
Gender	
Male	21
Female	16
Age (years)	
Median	60
Range	25–74
ECOG performance status score	
0	8
1	24
2	5
Histological type	
Intestinal type	
Well-differentiated tubular adenocarcinoma	4
Moderately differentiated tubular adenocarcinoma	7
Papillary adenocarcinoma	1
Diffuse type	
Poorly differentiated adenocarcinoma	6
Mucinous adenocarcinoma	2
Signet-ring cell carcinoma	17
Macroscopic type of primary tumor	
Scirrhous type	21
Non-scirrhous type	16
Metastatic sites	
Lymph nodes	25
Liver	7
Krukenberg's tumor	2
Douglas's metastasis	1
Lung	2
Bone	1
Pleural effusion	4

not improve within 8 weeks or when toxicity did not disappear within 6 weeks.

Response and Toxicity Evaluation

Tumor response was assessed by CT scan or ultrasonography of the target lesions every 4 weeks after the first administration of MTX. Complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were defined according to the response assessment criteria proposed by the Japanese Research Society for Gastric Cancer (17). The response in ascites was evaluated by abdominal CT scan or ultrasonography based on the following specific criteria used in this study: (1) disappearance of ascites – disappearance of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (2) decrease of ascites – apparent decrease of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (3) no response of ascites – no change of ascites volume visualized by CT scan or ultrasonography. The data for tumor response in all responders was confirmed by an extramural review. The toxicity was evaluated according to the JCOG common toxicity criteria (18).

Statistical Analysis

The sample size was determined based on the precision of the estimates. The efficacy for malignant ascites was expected to be 30%. Fifty subjects and an observed efficacy of 30% would provide a 95% confidence interval of 17.9–44.6% or width of 26.7%. The expected accrual period was 1.5 years. Interim analysis was planned to test for inefficacy of the treatment by examining whether a 90% upper confidence bound of efficacy would exceed 25% for first 20–25 patients. The overall survival was calculated for the period from the date of registration to the date of death. Overall survival was calculated by the Kaplan–Meier method and confidence intervals were calculated based on Greenwood's formula.

RESULTS

Patient Population and Study Treatment

Between February 1997 and October 1999, 37 patients were enrolled in this trial from nine out of 13 participating institutions. Although this study was originally planned as a phase II study in which 50 patients would be enrolled within 1.5 years of the start of the study, the patient enrollment was delayed and was finally terminated before the projected number of patients had been achieved based on the decision of the JCOG monitoring committee that the evaluation of efficacy and toxicity was possible even with only 37 enrolled patients. Table 1 lists the demographic data, baseline disease and pretreatment characteristics of all patients. Twenty-one males and 16 females were registered as receiving first-line chemotherapy. The median age of the patients was 60 years (range, 25–74 years) and the majority of the patients (86%) had a good performance status of 0–1. Twenty-one patients (57%) had macroscopically scirrhous-type advanced gastric cancer. Twenty-five patients had histologically diffuse types (six poorly differentiated adenocarcinoma, two mucinous carcinoma and 17 signet-ring cell carcinoma). Two patients had undergone surgery prior to enrollment in this trial (one palliative total gastrectomy and the other exploratory laparotomy resulting in no resection). One patient suffered from hemilateral hydronephrosis due to peritoneal dissemination with normal range of renal function tests.

In total, 355 administrations of the sequential MTX/5FU therapy were performed in 37 patients. The median number of administrations was eight (range, 1–42). Twenty-nine of 37 enrolled patients (78%) received at least four administrations of the sequential MTX/5FU therapy. All patients were assessable for toxicity and response of ascites to chemotherapy. Thirty-five patients were assessable for objective tumor

Table 2. Toxicity profiles

Toxicity	JCOG grade					Grade 4 (%)
	0	1	2	3	4	
Hematological toxicity						
Leukopenia	11	13	7	4	2	5.4
Neutropenia	17	5	5	6	4	10.8
Anemia	7	6	15	9	–	–
Thrombocytopenia	32	3	1	1	0	0
Non-hematological toxicity						
Nausea/vomiting	13	14	10	0	–	–
Diarrhea	25	4	6	2	0	0
Stomatitis	30	7	0	0	0	0
Alopecia	35	2	0	–	–	–
Allergic reaction	36	1	0	0	0	0
Fever	18	10	9	0	0	0
Peripheral neuropathy	36	1	0	0	–	–
Total bilirubin	20	–	8	8	1	2.7
AST	16	16	5	0	0	0
ALT	16	16	5	0	0	0
Alkaline phosphatase	16	17	2	2	0	0
Creatinine	33	2	0	2	0	0
Hyponatremia	12	17	7	0	1	2.7
Hypokalemia	21	12	4	0	0	0

response to chemotherapy. The most frequent reason for treatment termination was disease progression (27 patients, 73%). Other reasons for treatment termination were no response after 8 weeks from initiation of treatment in two, patient refusal in two, severe toxicity in two, death in three (one due to disease progression and two treatment-related) and medical judgment by the investigators in one.

TOXICITY

The toxicity observed in the study period is summarized in Table 2. The major toxicity was myelosuppression and gastrointestinal toxicity. Grades 3 and 4 neutropenia occurred in 16 and 11% of the patients, respectively. Severe thrombocytopenia was infrequent. The incidence of grade 3 diarrhea was 5%. Mild nausea and vomiting (grades 1 and 2) were frequently experienced (65%). An increase in total bilirubin of grade 4 was observed in one patient (2.7%) and was diagnosed as obstructive jaundice caused by the development of lymphadenopathy from the primary disease. An increase in total bilirubin grade 3 was observed in eight patients, three cases of which were judged to be treatment-related. An increase in serum creatinine grade 3 was observed in two patients (5.4%). One patient experienced grade 4 hyponatremia due to loss of oral intake associated with primary disease. Early death, which was defined as death within 30 days from the last administration of anti-cancer drugs, occurred in five patients. The causal relationship between the death and the study treatment was 'unlikely' in three of those five patients. However, the remaining two deaths were assessed to be treatment-related. One patient died of severe neutropenia and rapidly progressive disseminated intravascular coagulation (DIC), which was complicated with respiratory dysfunction, and the other patient died of progressive neutropenic sepsis.

EFFICACY

The efficacy-related data are summarized in Table 3. Only two of 35 response-assessable patients achieved objective partial response (response rate 5.7%; 95% confidence interval: 0.7–19.2%). However, in terms of the response of ascites, three disappearances and 10 decreases of ascites were obtained (response rate 35.1%; 95% confidence interval: 20.2–52.5%). The median duration of response of ascites was 103 days with a range of 52–337 days. The median survival time of all patients was 155 days (95% confidence interval: 131–225 days) and the 1 year survival rate was 16.2% (95% confidence interval: 4.3–28.1%).

DISCUSSION

Although unresectable or metastatic gastric cancer is potentially incurable, there is significant evidence that adding systemic chemotherapy to the best supportive care could provide benefits in survival and quality of life as compared with best supportive care alone (1–3). However, it has been difficult to assess which of many available regimens is the most effective, although several regimens have been tested in randomized controlled trials. Some randomized trials failed to demonstrate the superiority of 5FU-based combination regimens as compared with 5FU-monotherapy (19–21). A recent randomized controlled trial showed that three commonly used combination regimens, 5FU/adriamycin/MTX (FAMTX), 5FU/cisplatin (FP) and etoposide/leucovorin/5FU (ELF), have only modest activity and that there were no significant differences in overall survival among these regimens (22). More recently, infusional 5FU in combination with cisplatin and epirubicin (ECF) showed significant superiority over FAMTX in terms of response rate, quality of life and survival, suggesting that the ECF could be a new standard treatment for future clinical trials (23). However, regarding the median survival time in those large-scale trials, there was little substantial difference among the various regimens. Therefore, in general, 5FU-based or cisplatin-based combinations are widely accepted as a possible standard therapy (24). In clinical practice, oncologists need to select a regimen considered to be the most appropriate for each individual patient based on the medical condition of each patient, including such factors as age, performance status, organ function and extent of disease. The cisplatin-based regimens are usually inappropriate to be used for patients having peritoneal dissemination and retention of ascites, because such patients have potential renal impairment or poor performance

Table 3. Responses to treatment (total of 355 administrations of the sequential MTX/5FU therapy)

	No. of evaluable patients	CR	PR	NC	PD	NE	Response rate (%)	95% CI (%)
Objective response	35	–	2	21	6	6	5.7	0.7–19.2
Response in ascites	37	3	10	15	6	3	35.1	20.2–52.5

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.

status, which makes it difficult to tolerate the large volume hydration for the prevention of cisplatin-induced renal injury. Among several 5FU-based regimens, sequential MTX/5FU therapy is widely used because this regimen has definite anti-tumor activity against advanced gastric cancer with acceptable toxicity even in high-risk patients. The purpose of the present phase II study was to evaluate the efficacy and toxicity of the sequential MTX/5FU regimen in patients with unresectable gastric cancer with peritoneal dissemination accompanied by malignant ascites and to assess whether further investigation in a phase III setting is warranted.

Progression to peritoneal dissemination is very common in advanced gastric cancer and is frequently a component of the first episode of failure after surgery for primary gastric cancer (25). Therefore, intraperitoneal chemotherapy has previously been investigated for peritoneal dissemination for the purposes of palliation and the prevention of peritoneal metastasis after surgery in high-risk patients. The pharmacokinetic rationale for intraperitoneal therapy is that drug concentrations within the peritoneal cavity are several-fold to 1–2 logs higher than concentrations that can be achieved after oral or intravenous treatment (26,27). In ovarian cancer, a large randomized trial demonstrated a small but statistically and clinically significant survival advantage in patients receiving intraperitoneal therapy (28). However, generally the efficacy of intraperitoneal chemotherapy is considered to be modest because the penetration of intraperitoneally injected drug into submesothelial tissue is too limited to achieve anti-tumor activity. Moreover, intraperitoneal chemotherapy sometimes induces systemic adverse events similar to systemic chemotherapy in addition to local complications such as chemical peritonitis. No definite data are currently available to specify which treatment option, intraperitoneal or systemic chemotherapy, is more suitable for patients with peritoneal dissemination in terms of benefit regarding survival and quality of life.

When we perform systemic chemotherapy in patients who have fluid retention such as ascites or pleural effusion, we have to consider the pharmacokinetic alterations of the anti-tumor agents administered. Intravenously administered MTX penetrates the ascites or pleural effusion and the clearance rate of MTX from ascites and plasma is ~5 and ~120 ml/min, respectively (29). Therefore, the retention of body fluid prolongs the terminal plasma half-life of intravenously administered drug owing to the slow re-entry of the sequestered drug into the bloodstream. Such phenomena should be associated with both favorable anti-tumor activity against peritoneal or pleural dissemination and with the potential risk of systemic toxicity. In another phase II study of sequential MTX/5FU therapy against unresectable or metastatic gastric cancer previously conducted by the JCOG, in which the same dosage and schedule as in the present study were utilized but the patients having ascites were ineligible for entry (JCOG 9207 study), none of 56 enrolled patients experienced grade 3 or 4 neutropenia (data not shown). In the present study, grades 3 and 4 neutropenia were observed in six (16 %) and two patients (11 %), respectively. The incidence of leukopenia, anemia, increase in total bilirubin and increase in serum creatinine of grade 3 or 4 tended to be more frequent in the present study than in the JCOG 9207 study (data not shown). Therefore, the toxicity of the sequential MTX/5FU therapy might be more severe in patients with malignant ascites than in those without. Two treatment-related deaths were observed in the present study. These two patients developed progressive neutropenic sepsis, which is a major cause of death. Although these two patients had met the eligibility criteria required in the study, both patients were retrospectively shown to be at high-risk for neutropenic infection, because pretreatment serum CRP values were highly elevated in both patients and leukocytosis was also observed at the baseline in one patient. Therefore, we consider that patients with apparent inflammatory signs such as elevation of CRP or leukocytosis should be excluded from future studies to prevent neutropenic sepsis. It is known that the different methods of administration of 5FU, either as a bolus or by infusion, represent different efficacy and toxicity profiles, thus infusional 5FU has more clinical benefit in efficacy (response rate) and safety in metastatic colorectal cancer. At present, however, we do not have sufficient data to establish whether these clinical observations hold true in patients with peritoneal dissemination with malignant ascites and it seems to be important to investigate the infusional 5FU-based regimens in this clinical setting, which may contribute to reducing the toxicity.

It is difficult to evaluate the efficacy of chemotherapy against peritoneal dissemination in clinical trials as well as in clinical practice, because most disseminated tumor cells do not form a measurable mass but rather constitute a diffuse lesion. Clinicians have to assess the efficacy of treatment and disease status in each patient based on the integration of clinical information such as clinical imaging, tumor markers and clinical symptoms. In the present study, the therapeutic efficacy was assessed according to the specific criteria for the study based on the change in the volume of ascites visualized by abdominal CT scan or ultrasonography as a surrogate marker. Using these criteria, we found that the ascites disappeared or was decreased by the MTX/5FU therapy in 35% of the patients. Konishi et al.

also reported that ascites disappeared in 50% (8/16) of patients with peritoneal-disseminated gastric cancer after MTX/5FU therapy (16). These results show that sequential MTX/5FU therapy is effective in controlling malignant ascites and also suggest that this regimen is effective against peritoneal dissemination from advanced gastric cancer.

Although the present study was originally planned as a phase II study involving 50 patients, patient enrollment had been delayed and finally terminated before the projected number of patients was achieved. The delay in patient enrollment was probably caused by the eligibility criteria for this study. Although peritoneal dissemination of advanced gastric cancer is very common in clinical practice, most patients with peritoneal dissemination accompanied by malignant ascites tend to have relatively poor performance status and impaired organ function, which was considered to be a critical issue delaying patient enrollment. The JCOG monitoring committee accepted the investigators' decision that the objectives of this study, which were to calculate the response rate in ascites and to evaluate the safety of sequential MTX/5FU therapy for decision-making to pursue further investigation in a phase III study, were achieved even with the actual sample size of 37 patients and that the response rate in ascites of 35% (95% confidence interval: 20.2–52.5%) observed in this study was positive.

It is well known that peritoneal dissemination of gastric adenocarcinoma occurs more commonly as the histologically diffuse type than the intestinal type. Konishi et al. reported that sequential MTX/5FU therapy was more effective against undifferentiated gastric cancer (i.e. histologically diffuse type) than differentiated gastric cancer (i.e. histologically intestinal type), with a response rate of 32% (9 PRs/28 patients) vs 0% (0 PRs/10 patients) (16). A similar tendency was observed in the present study, namely that the response rate of ascites was higher for the histologically diffuse type than for the intestinal type (44%, 11 responders among 25 patients, versus 17%, two responders among 12 patients). The difference in the efficacy of the sequential MTX/5FU therapy depending on the histological type might be explained by the difference in the activities of two enzymes, thymidylate synthetase and thymidine kinase, in the various histological types of gastric cancer (30). However, other reports have suggested that there were no significant differences according to the histological type. (15)

In conclusion, the findings of the present study suggest that sequential MTX/5FU therapy is effective in controlling malignant ascites from gastric cancer with overall acceptable toxicity and that further investigations are warranted. However, the present study also suggests that severe toxicity may occur more frequently in patients with malignant ascites than in those without malignant ascites. Whether there is true clinical benefit in this regimen for patients with peritoneal dissemination from advanced gastric cancer should be evaluated in future randomized clinical trials. Since the peritoneal dissemination from gastric cancer is considered to be an incurable disease, the patient's survival and quality of life will be important endpoints to be assessed in the future clinical trials. Recently, various new drugs with different mechanisms of action have been developed. However, since the patients whose main diseases are peritoneal dissemination are usually excluded from the phase II trials of new drugs or new combination regimens because of the lack of measurable lesions in those patients, the available data as to the efficacy against peritoneal dissemination are very limited unless we conduct trials specifically designed for this purpose as the present study. We think it is important to assess the roles of new drugs from the viewpoint of how we can maximize the potential value of each drug or regimen in disease-specific clinical situations. In this study we have focused on peritoneal dissemination with malignant ascites from advanced gastric cancer, which is very common and a major clinical problem. At present, any 5FU-based combination chemotherapies cannot prolong overall survival compared with 5FU alone. However, the present study brought us to the hypothesis that if we choose an appropriate regimen and administer it to the appropriate patient population (for example, to choose MTX/5FU therapy for the patients with peritoneal dissemination), survival may be prolonged compared with 5FU alone. We think that MTX/5FU therapy is the most reasonable regimen to be tested as a first-line chemotherapy in patients with peritoneal dissemination from advanced gastric cancer. From this clinical standpoint, a phase III randomized controlled trial comparing sequential MTX/5FU therapy with infusional 5FU-monotherapy (800 mg/m^2 of 5FU continuous infusion over 5 days every 4 weeks) in patients with advanced gastric cancer who have peritoneal dissemination with or without ascites is currently being carried out by the Japan Clinical Oncology Group (JCOG 0106-MF study). As a final note, we suggest that in future trials we should investigate the therapeutic strategy not only with newer cytotoxic drugs including irinotecan, taxanes and oxaliplatine, but also with new molecular targeting drugs such as antibody, VEGF drugs and EGF drugs, to bring about a breakthrough in this dire clinical condition.

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Long-term Survival and Prognostic Factors in Patients with Metastatic Gastric Cancers Treated with Chemotherapy in the Japan Clinical Oncology Group (JCOG) Study

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Background: The long-term survival of patients after chemotherapy for advanced gastric cancer remains unclear. The aim of this analysis was to investigate prognostic factors for patients with metastatic gastric cancer treated by chemotherapy, and to identify the characteristics of long-term survivors.

Methods: Six hundred and forty three patients were enrolled in four phase II studies and one phase III study by the Japan Clinical Oncology Group between January 1985 and April 1997. By adjusting patients' eligibility between the five studies, 497 patients (77%) were selected for the analysis. Univariate and multivariate analyses were performed using log-rank tests and Cox's proportional hazard model, respectively.

Results: Of the 497 patients analyzed, 39 (8%) and 11 (2%) patients have survived longer than 2 and 5 years, respectively. By multivariate analysis, better performance status, a small number of metastatic sites and macroscopically non-scirrhous type tumors were significantly associated with better prognosis. Characteristics of the 11 5-year survivors revealed eight with para-aortic node metastases alone. Eight of these patients received gastrectomy; four underwent it before chemotherapy, and the other four patients received it after achieving downstaging with successful chemotherapy.

Conclusions: These results demonstrated that better performance status, a small number of metastatic sites and macroscopically non-scirrhous type tumors are independent favorable factors for survival. There were a few 5-year survivors with unresectable gastric cancers, most of whom had only abdominal lymph node metastases and received gastrectomy before or after chemotherapy.

Key words: gastric cancer – chemotherapy – long-term survival – prognostic factors

INTRODUCTION

Gastric cancer remains one of the major leading causes of death worldwide. For unresectable advanced or recurrent gastric cancers, systemic chemotherapy has marginal survival benefits as compared with best supportive care (1–4), though it has only palliative impact. Over the past 20 years, many chemotherapeutic agents—often as combination regimens—have been studied in gastric cancer. Although there have been some recent reports of very high response rates with the newer combination regimens, no standard regimens have been established, and the median survival time of patients with advanced gastric cancer still remains <1 year. In each of the phase II and phase III studies, outcomes have usually been evaluated as median survival times and 1- or 2-year survival rates. However, there have been few multivariate analyses based on a sufficient number of patients to evaluate the impact of chemotherapy, when combined with prognostic factors, on long-term survival of patients with metastatic gastric cancers.

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Between 1985 and 1997, the Japan Clinical Oncology Group (JCOG) carried out one randomized phase II study, three series of phase II studies and one randomized phase III study, for ~600 patients with unresectable gastric cancer (5–9). Although some combination regimens have been attempted in our group, no regimens have demonstrated survivals significantly superior to those with the single agent 5-fluorouracil (5-FU). Before initiating the last phase III study, we reported (10) the preliminary long-term results of the 226 patients enrolled, which revealed 2- and 5-year survivals of 10 and 4%, respectively. However, the number of patients in that analysis was too small to clarify long-term survival and to carry out multivariate analysis for prognosis. We have now re-analyzed the long-term survivals using multivariate analysis, after obtaining long-term outcomes with a minimum follow-up period of 5 years for patients registered in the large multi-institutional phase III study. The aim of this analysis was to clarify the impact of chemotherapy on long-term results and prognostic factors in patients with unresectable advanced and recurrent gastric cancers.

PATIENTS AND METHODS

PATIENT SELECTION

Between January 1985 and April 1997, 643 patients were enrolled in four phase II and one phase III JCOG study (study numbers 8501, 8804, 8903, 9001 and 9205, listed in Table 1). The chemotherapy consisted of the following six regimens: (i) tegafur 500 mg/m^2 per day on days 1–28 + mitomycin C 5 mg/m^2 per day on days 1, 8, 15 and 22 every 4 weeks (FTM); (ii) uracil-tegafur 375 mg/m^2 per day on days 1–28 + mitomycin C 5 mg/m^2 per day, on days 1, 8, 15 and 22 every 4 weeks (UFTM); (iii) 5′-doxifluridine 1400 mg/m^2 per day on days 1–4 and 15–18 + cisplatin 80 mg/m^2 per day on day 5, every 4 weeks (5′P); (iv) etoposide 100 mg/m^2 per day on days 4–6 + doxorubicin 20 mg/m^2 per day on days 1 and 7 + cisplatin 40 mg/m^2 per day on days 2 and 8, every 4 weeks (EAP); (v) 5-FU 800 mg/m^2 per day on days 1–5 + cisplatin 20 mg/m^2 per day on days 1–5, every 4 weeks (FP); and (vi) continuous infusion of 5-FU 800 mg/m^2 per day on days 1–5, every 4 weeks (5-FUci). In the earlier studies (8501 and 8804), patients with potentially resectable cancers were included, because patients whose medical complications made surgical intervention unsuitable were accepted as eligible. To adjust the patients' eligibility between the five studies, 497 (77%) patients who met the following criteria were selected from the 643 case report forms: (i) histologically proven adenocarcinoma of the stomach with measurable or evaluable lesions; (ii) evidence of unresectable disease, organ metastasis, distant node metastasis, peritoneal dissemination detected by barium enema or laparotomy, or involvement of the adjacent organs confirmed by laparotomy; (iii) age ≤75 years; (iv) performance status (PS) on the Eastern Cooperative Oncology Group scale of 0–2; (v) adequate organ functions; (vi) no serious complications; (vii) no other active malignancies; and (viii) no prior chemotherapy. Characteristics of the 497 patients are listed in Table 2.

Table 1. Clinical outcomes of each chemotherapy regimen

Study no.	Regimen	*n*	RR	MST	2-year survival (%)	5-year survival (%)
8501	FTM	50	8	6.0	2 (4)	0
	UFTM	39	21	7.1	1 (3)	1 (3)
8804	5′P	49	35	8.1	8 (16)	2 (4)
8903	EAP	42	55	9.3	6 (14)	3 (7)
9001	FP	46	43	7.4	5 (11)	2 (4)
9205	UFTM	67	9	6.0	3 (4)	0
	FP	100	36	7.7	7 (7)	0
	5-FUci	104	12	6.7	7 (7)	3 (3)

RR = response rate; MST = median survival time (months). See text for the definitions of the regimens.

Table 2. Patient characteristics

	n = 497
Age (years): median (range)	61 (19–75)
Gender: male/female	364/133
PS: 0/1/2	175/236/86
Histological types: I/D/U	228/266/3
Macroscopic types: scirrhous/non-scirrhous	137/362
History of gastrectomy: +/−	84/413
Metastatic site	
Liver	236
Abdominal lymph node	232
Peritoneum	86
Others	70
No. of metastatic sites: 1/2/≥3	315/148/34

I/D/U = intestinal/diffuse/unknown; PS = performance status.

EVALUATION OF RESPONSES

Responses to chemotherapy were evaluated according to the standard World Health Organization criteria for measurable metastatic lesions (11). For primary lesions, the responses were evaluated according to the criteria proposed by the Japanese Research Society for Gastric Cancer (12) using either gastroscopy or barium gastrography. The responses to chemotherapy were confirmed by extramural review during each study and were adopted into the present analysis according to each case report form. Overall response was defined as the sum of the number of complete and partial responses.

STATISTICS

Survival times of all patients were calculated from the date of registration to the date of death from any cause, or to the last confirmation of survival, using the Kaplan–Meier method.

Of the 497 patients, only four (1%) patients were lost to follow-up. Survival was updated in February 2002, with a minimum follow-up period of 5 years for univariate and multivariate analyses. Univariate analyses were performed by log-rank testing using the following seven categories: (i) age >60 versus ≤60 years old; (ii) male versus female; (iii) PS 0 versus 1 or 2; (iv) macroscopically scirrhous-type cancer (Japanese classification type 4) versus non-scirrhous type; (v) histologically intestinal type versus diffuse type; (vi) with versus without history of gastrectomy; and (vii) one versus two versus three or more metastatic sites. Multivariate analysis of prognostic factors using a Cox proportional hazard model was carried out with these categorized variables to calculate relative risks and their 95% confidence intervals (CIs).

RESULTS

Patient Characteristics

Characteristics of the 497 patients are summarized in Table 2. Most of the patients had a good PS at registration, while 86 (17%) had a PS of grade 2. Histologically, 228 (46%) patients had an intestinal type of adenocarcinoma, 266 (54%) had a diffuse type and three had an unknown type. One hundred and thirty-seven patients (28%) had macroscopically scirrhous-type primary gastric tumors. Eighty-four (17%) patients had undergone gastrectomy before registration. The sites of metastases documented in the 497 case report forms were: abdominal lymph nodes in 232 (47%); liver in 236 (47%); peritoneum in 86 (17%), and others in 70 (14%) patients. The number of metastatic sites consisted of one in 315 (63%), two in 148 (30%) and three or more in 34 (7%) patients, respectively.

Response and Survival

Of the 497 patients, six (1%) achieved a complete response (CR) and 121 (24%) achieved partial responses, giving an overall response rate of 26%. The response rates in each regimen are listed in Table 1, ranging from 8% in the FTM group to 55% in the EAP group. Figure 1 shows survival curves of all 497 patients, indicating a median survival time (MST) of 7.2 months. The MSTs in each regimen are listed in Table 1, ranging from 6.0 to 9.3 months. Of the 497 patients, 39 (8%) and 11 (2%) have survived longer than 2 and 5 years, respectively. The numbers of 2- and 5-year survivors in each regimen are listed in Table 1.

Characteristics of Long-term Survivors

Twenty-six (67%) of the 39 2-year survivors responded to the initial chemotherapy. These 39 patients included 11 with para-aortic node metastasis alone as an 'unresectable factor'. All of the 39 patients had been classified into PS grades 0 or 1 at registration. Twelve patients had prior gastrectomy before starting chemotherapy. There were no significant differences in histological types between the 2-year survivors and the others.

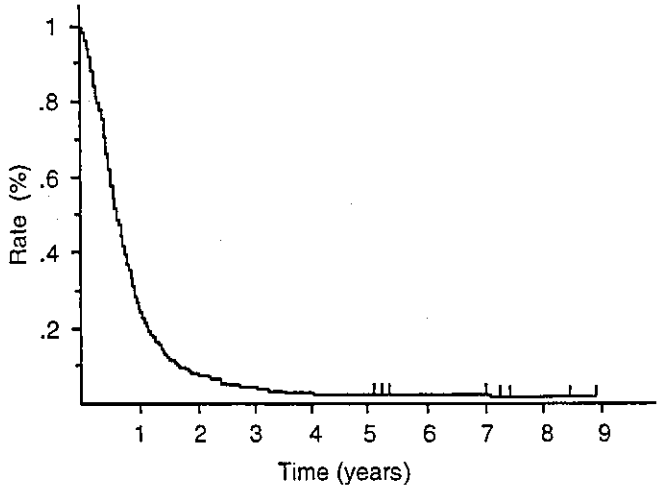

Figure 1. Overall survival of patients.

Table 3. Characteristics of 5-year survivors

Age	G	PS	Macro	H	MS	Surg.	First R	Response 1st/2nd	Surv	Pre
75	M	0	N	D	Liver	–	5-FUci	CR/–	60	D
65	M	0	N	I	A-LN	B	5-FUci	PR/PR	61	A
46	M	0	N	D	A-LN	B	5-FUci	PR/–	63	A
55	M	1	N	I	Liver	–	UFT	PR/CR	65	A
47	M	0	N	I	A-LN	B	FP	CR/–	85	A
52	M	1	N	I	A-LN	–	5'FP	CR/–	86	D
57	M	1	N	D	A-LN	A	EAP	PR/–	87	D
53	M	0	N	D	A-LN	A	EAP	CR/–	88	A
49	F	0	N	D	A-LN	B	FP	NC/CR	90	A
58	M	0	N	I	A-LN, C-LN	A	EAP	CR/–	103	A
62	M	1	N	I	A-LN	A	5'FP	PR/–	108	A

G = gender; M = male; F = female; PS = performance status; Macro = macroscopic type; N = non-scirrhous; H = histology; I = intestinal; D = diffuse; MS = metastatic site; A-LN = abdominal lymph node; C-LN = cervical lymph node; Surg. = surgical resection (A = after chemotherapy; B = before chemotherapy); R = regimen (for definitions see text); CR = complete response; PR = partial response; Surv = survival (months); Pre = present status (A = alive; D = dead).

Characteristics of the 11 5-year survivors are summarized in Table 3. These patients consisted of eight with para-aortic node metastases alone as an 'unresectable factor', one with para-aortic and cervical node metastases, and two patients with only liver metastases. Ten of the 11 patients achieved overall responses to the initial chemotherapy: five patients achieved CR at the initial chemotherapy and one patient achieved CR by the second-line chemotherapy. One patient, who had not achieved an objective response to the initial chemotherapy (FP) achieved CR in the third line chemotherapy, consisting of 5-FU + doxorubicin + mitomycin C. Of the 11, eight patients received surgical resections, four patients before initiating the chemotherapy and four after achieving tumor regression

Table 4. Univariate analysis by each variable

Variable	n	MST	2-year survival (%)	5-year survival (%)	P-value
Age (years)					
<60	219	7.8	10.5	3.7	
≥60	278	6.8	5.8	1.1	0.04
Gender					
Male	364	7.2	8.2	2.7	
Female	133	7.2	6.8	0.8	0.9
Performance status					
0	175	9.9	11.0	4.0	
1	236	6.8	8.5	1.7	
2	86	5.1	0	0	<0.01
Histological type					
Intestinal	228	7.8	9.2	2.6	
Diffuse	266	6.5	6.8	1.9	0.3
Macroscopic type					
Scirrhous	137	6.0	4.4	0	
Non-scirrhous	360	7.6	9.2	3.1	0.04
History of gastrectomy					
Yes	84	8.3	14.3	4.8	
No	413	6.8	6.5	1.7	0.02
No. of metastatic sites					
1	315	8.3	9.5	3.2	
2	148	5.9	5.4	0.7	
≥3	34	5.4	2.9	0	<0.01

Table 5. Relative risk of prognostic factors

Variable	n	RR	95% CI	P-value
Age (years)				
<60	219	–		
≥60	278	1.16	0.97–1.40	0.2
Gender				
Male	364	–		
Female	133	0.93	0.75–1.14	0.5
Performance status				
0	174	–		
1	235	1.16	1.08–1.25	<0.01
2	85			
Histological type				
Intestinal	228	–		
Diffuse	266	1.13	0.97–1.30	0.11
Macroscopic type				
Scirrhous	137	–		
Non-scirrhous	360	1.27	1.02–1.25	0.04
History of gastrectomy				
Yes	84	–		
No	413	1.01	0.92–1.10	0.9
No. of metastatic sites				
1	315	–		
2	148	1.32	1.14–1.53	0.01
≥3	34			

Performance status and no. of metastatic sites are ordered categories.

in the initial chemotherapy, including two with a pathological CR in the surgically resected specimen. The remaining three patients did not receive surgical resection during the follow-up period. Ten of the 11 5-year survivors presented with no evidence of disease at 5 years, while two patients died after 5 years because the primary disease recurred.

Univariate and Multivariate Analyses

Results of the univariate and multivariate analyses are summarized in Tables 4 and 5. Univariate analysis revealed significantly better survival in patients in five categories: age <60 years, PS = 0, macroscopically non-scirrhous-type tumors, a prior history of gastrectomy and a small number of metastatic sites. Figure 2 shows the survival curves of the patients with only one metastatic site: 77 with abdominal lymph nodes, 44 with peritoneal tumors and 117 with liver metastases alone. Their MSTs were 9.6, 8.2 and 7.7 months, with 2-year survival rates of 14.3, 15.9 and 6.8%, and with 5-year survival rates of 10.4, 0 and 1.7%, respectively. One hundred and seventeen patients with only liver metastases had the worst MST among the three groups and showed significantly poorer survivals than the remaining patients ($P = 0.04$). Seventy-seven patients with only abdominal lymph node metastases had a remarkably higher 5-year survival rate than other groups, while their MSTs and 2-year survival rates were similar to those of 44 patients with only peritoneal metastases.

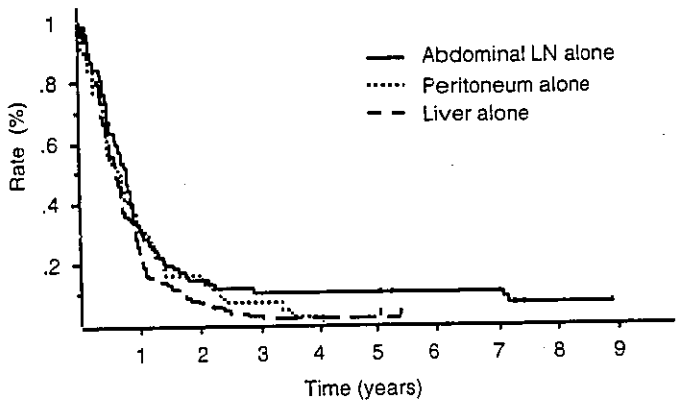

Figure 2. Survival of patients with a single metastatic site: 77 patients had a metastasis to an abdominal node, 117 had a liver metastasis and 44 had a peritoneal metastasis. LN, lymph node.

Multivariate analysis revealed that the presence of only one metastatic site, a macroscopically non-scirrhous-type tumor

and a good PS score were each significantly associated with better prognosis (Table 5).

DISCUSSION

We have already reported the preliminary long-term results of 226 patients with unresectable gastric cancer and treated with systemic chemotherapy, which revealed 2- and 5-year survivals of 10 and 4%, respectively (10). In the present analysis, an additional 271 patients registered in the subsequent phase III trial (9205) were included to confirm the previous results and to carry out multivariate analysis for prognosis. With regard to the long-term results, 2- and 5-year survivals in the additional 271 patients were 6 and 1%, respectively. These survivals were lower than those obtained previously (10), where long-term survivals in cisplatin (CDDP)-containing regimens (8804, 8903 and 9001) were better than non-CDDP-containing regimens (8501). One possible reason for the lower long-term survivals in trial 9205 might be that only one of the three arms included a CDDP-containing regimen (FP). However, this superiority of a CDDP-containing regimen was not observed in the additional 271 patients enrolled into the phase III study (9205): 2- and 5-year survivals in the FP group were 7 and 0%, whereas those in the 5-FUci group were 7 and 3%, respectively. Based on these results, the superiority of CDDP-containing regimens in the phase II series (8804, 8903 and 9001) in terms of long-term survival might have been caused by selection bias: for example, the incidence of patients with a single metastatic site was 77% in phase II and 52% in phase III.

Was the long-term survival of a few patients truly achieved by chemotherapy, or was it simply related to the natural history of these patients? Because there have been no prospective reports using adequate sample sizes on the long-term survival of patients not treated with chemotherapy, it is hard to establish the effectiveness of chemotherapy for long-term survival. However, there have been two randomized trials comparing best supportive care with combination chemotherapy (1,2). Although these studies had only a few patients, no patient treated solely with supportive care survived longer than 1 year. Additionally, most of the long-term survivors in the present analysis achieved good responses to chemotherapy, particularly the 5-year survivors: 10 of the 11 patients were alive with no evidence of disease at 5 years. These results thus support the value of chemotherapy for achieving long-term survival.

Because the case report forms in the earlier study frequently lacked laboratory reports of serum data including tumor markers, these data were excluded from this multivariate analysis. Univariate analysis revealed that there were significant differences in survival in terms of PS grade, numbers of metastatic sites, having a history of gastrectomy, age and macroscopic tumor type. However, multivariate analysis showed there were only three variables significantly and independently associated with a good prognosis: having a better PS grade, having fewer metastatic sites and the presence of macroscopically non-scirrhous-type tumors. Better PS grade and fewer metastatic sites are also known to be better prognostic factors in patients with advanced colorectal cancer treated with chemotherapy (13). In addition, patients with macroscopically scirrhous-type tumors showed significantly poorer survival than those with non-scirrhous types, and this seems to be specific for patients with gastric cancers. Scirrhous tumors are also known to lead to poorer survival than other macroscopic types in patients treated by surgical resection (14). Thus, these forms of tumors appear to be especially malignant and exhibit a higher resistance to chemotherapeutic agents.

Another objective of this study was to clarify the characteristics of the long-term survivors. The 11 5-year survivors had some specific characteristics. All patients had good PS grades of 0 or 1 and macroscopically non-scirrhous-type tumors. Ten had only one metastatic site, achieved a CR through the initial chemotherapy and had no evidence of disease at 5 years. Another significant characteristic was that eight of the patients had only a para-aortic node metastasis as an unresectable factor. In the whole study series, 77 such patients had significantly better 5-year survival (10.4%) than the other patients with single metastatic sites, such as in the liver or peritoneum. Thus patients with para-aortic node metastases alone have a greater chance of achieving long-term survival than other patients; this suggests that potentially curative strategies such as adjuvant surgery may be effective for them. A phase II study of this strategy for this subpopulation (neoadjuvant chemotherapy followed by surgery) by the JCOG is now underway.

The role of surgery in patients with potentially incurable disease remains controversial. Although patients with prior surgery showed better survival than others in the univariate analysis, this was not found in the multivariate analysis. This might have been caused by 'leading bias'—early detection of recurrence—because of periodic follow-up surveys after surgery. It is also difficult to evaluate the role of adjuvant surgery after achieving downstaging by chemotherapy because of the small number of such cases. However, of the 11 5-year survivors, eight received surgical resections for primary sites, including four patients with adjuvant surgery. Thus adjuvant surgery might have value, particularly for patients with para-aortic node metastasis alone, if they achieve downstaging by chemotherapy. Of course, these advantages should be evaluated further in the ongoing neoadjuvant study.

In conclusion, there were a few long-term survivors in patients with unresectable gastric cancer treated with chemotherapy. This suggests that some patients with only abdominal lymph node metastases may achieve long-term survival with successful chemotherapy. Better PS scores, small numbers of metastatic sites and macroscopically non-scirrhous-type tumors were independent favorable factors for survival in the multivariate analysis.

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SHORT COMMUNICATION

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Existential concerns of terminally ill cancer patients receiving specialized palliative care in Japan

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Abstract *Background:* Although alleviation of existential distress is important for terminally ill cancer patients, the concept of existential distress has not been fully understood. The aim of this study was to categorize existential concerns of Japanese terminally ill cancer patients and explore care strategies based on the categorizations. *Methods:* A multicenter cross-sectional study in 88 terminally ill cancer patients receiving specialized inpatient palliative care was performed. The nurses explored patient existential concerns by asking several key questions, and recorded the answers that they considered typically described the patients' concerns. All statements recorded by the nurses were analyzed using content analysis methods. *Results:* A total of 89 statements were subjected to analysis. The categories and their prevalence were: relationship-related concerns (22%; isolation, concerns about family preparation, conflicts in relationship), loss of control (16%; physical control, cognitive control, control over future), burden on others (4.5%), loss of continuity (10%; loss of role, loss of enjoyable activity, loss of being oneself), uncompleted life task (6.8%), hope/hopelessness (17%), and acceptance/preparation (25%). *Conclusions:* Existential concerns of Japanese terminally ill cancer patients were categorized as relationship-related concerns, loss of control, burden on others, loss of continuity, uncompleted life task, hope/hopelessness, and acceptance/preparation. These themes seemed to encompass universal human suffering beyond cultural differences, and this conceptualization may contribute to the development of effective therapeutic interventions to alleviate existential distress.

Keywords Existential distress · Spiritual care · Palliative care · Neoplasms

Introduction

Comprehensive care to alleviate the existential distress of terminally ill cancer patients is one of the main focuses of recent medical literature [1, 12]. Empirical studies have suggested that terminally ill cancer patients have a variety of existential concerns, associated with serious psychological morbidity such as desire for death and suicide [3, 5, 8, 9, 18, 23]. Existential distress described in the literature includes hopelessness, dependency, loss of control, loss of self-continuity, relatedness/isolation, meaninglessness, and loss of dignity [2, 3, 5, 6, 7, 8, 9, 14, 15, 18, 21, 23]. However, these concepts have not been fully supported by empirical data, and few studies have been performed in Japan [11, 16, 22]. Therefore, the primary aim of this study was to categorize existential concerns of Japanese terminally ill cancer patients and explore effective care strategies based on the categorizations.

Subjects and methods

This was a database survey on consecutive terminally ill cancer patients admitted to one of the four palliative care units of the Japanese Association of Hospice and Palliative Care Units.

The nurses were requested to explore patient existential concerns by asking several key questions: "What is your greatest concern?", "Are there any concerns about your family?", "What is the most important thing for you now?", "What is your goal or expectation?", and "Do you have any concerns about the future?". Then the nurses recorded the answers that they considered typically described the patients' concerns. This assessment was completed within a week after admission as part of daily practice, and no structured interview format or tape-recording methods were used. Religious concerns were not specifically addressed, because our primary interests were existential distress rather than religious distress, and many Japanese have no specific religion.

All statements recorded by the nurses were analyzed using content analysis [13]. Concerns were defined as needs or distress expressed by the patients. First, two groups each of two raters independently categorized these statements with regard to similarities and differences in their meanings in the context, and discordance was then resolved through discussion. The raters were a palliative care physician (principle investigator), a hospice nurse, and two nurses from the academic institution who participated in another qualitative study to investigate the spirituality of Japanese terminal patients [11]. The validity of the categorization was confirmed by consensus of the authors. The percentages of the total number of patients who expressed concerns in each category were calculated.

Ethical and scientific validity was confirmed by the institutional review boards of each hospital.

Results

Of 211 patients enrolled in the original database survey, 123 were excluded from analysis due to cognitive impairment, inability to communicate verbally, and/or no data recorded. We therefore obtained a total of 89 statements from 88 patients. The median age of the patients was 66 years (range 25–94 years), and 58 (66%) were male. Primary tumor sites were: colon/rectum (17), lung (15), liver/bile duct/pancreas (15), stomach (13), genitourinary (10), head and neck (7), breast (3), and others (8). The ECOG performance statuses were: 1 or 2 (15), 3 (38) and 4 (35). The diagnosis of malignancy was explicitly disclosed in 80 patients (91%).

Table 1 Existential concerns of Japanese terminally ill cancer patients

	Prevalence (%)
Relationship-related concerns	22 (n=19)
Isolation	
Concerns about family preparation	
Conflicts in relationship	
Loss of control	16 (n=14)
Physical control (dependency)	
Cognitive control	
Control over future (uncertainty)	
Burden on others	4.5 (n=4)
Loss of continuity	10 (n=9)
Loss of role	
Loss of enjoyable activity	
Loss of being oneself	
Uncompleted life task	6.8 (n=6)
Hope/hopelessness	17 (n=15)
Acceptance/preparation	25 (n=22)

Table 1 summarizes the categories identified and the prevalence rates. A total of 7 categories and 13 subcategories were identified. Existential concerns related to relationship were: (1) isolation, (2) concerns about family preparation, and (3) conflicts in relationship. Isolation was expressed as the patients' need for being with or receiving support from their loved ones, generally family members, such as "I feel lonely and want my wife to be close to me" and "my wife is a big support for me. I want her to be always with me". Concerns about their family preparation included patients' concerns about the family's preparation for the patient's death and the family's life after the patient's death, such as "I worry how my wife will get along after I die" and "I worry about the future of my son". Conflicts in relationship means a practical problem in the patient-family relationship, such as "I have concerns about the relationship with my (common-law) husband and children".

The category loss of control was classified into three subcategories: physical control, cognitive control, and control over one's future. Loss of physical control was related to inability of self-care and daily activity, typically expressed as "I feel shameful when I become unable to do things that I have always done myself". Loss of cognitive control was related to lowered mental activity, expressed for example as "I would rather die if I have to use morphine and remain half unconscious, not knowing whether I am alive or dead". Loss of control over one's future was related to distress from the uncertainty of when death would come, what would happen, and uncertainty about the dying process, such as "I am seized with thoughts of when and how death will come to me" and "I am confused, because I just don't see how things will turn out in the future".

Burden on others was typically expressed as "I just want to drop dead one day without bothering my family", which was associated with both relationship and loss of physical control. Loss of continuity was expressed as the patients' need to maintain their role and enjoyable activity, and to be themselves as they had been, such as "I want to go back to missionary work again to help others", "I want to enjoy living here, since I can feel alive most when I am talking like this", and "I want to live in my own way".

Uncompleted life task was recognized by patient expressions indicating that they had work, hobbies, legal affairs to arrange and funerals to be completed before death, such as "I have things to tell my family about, like the house and the work." Hope/hopelessness included broad areas of patient life, such as completion of a new house, birth of a child, the ballet show of a grandchild, returning home, and cure of the disease. Existential concerns related to acceptance/preparation were seen in patients who did not accept the imminence of death, did not sufficiently prepare for death, or felt significant death anxiety, typically stated as "I don't want to die" and "I fear that I am going to die".

Discussion

This study is the first to categorize existential concerns expressed by non-selected Japanese terminally ill cancer patients. A total of seven categories of existential concerns were identified: relationship-related concerns, loss of control, burden on others, loss of continuity, uncompleted life task, hope/hopelessness, and acceptance/preparation. These are generally consistent with a previous qualitative study about spirituality in Japanese, a preliminary observational study from a single Japanese inpatient hospice, and many empirical studies from Western culture [2, 4, 11, 14, 15, 16, 19, 20, 21]. This suggests that the themes identified in this study are universal aspects of human suffering beyond cultural differences.

Previous studies illustrate relationship-related concerns as a single term such as "maintaining relationships", "social support", "relations", "relational pain/abandonment", and "someone to talk to" [2, 4, 11, 14, 15, 19, 21]. This study suggests, however, that a further subcategorization of isolation, concerns about family preparation, and conflicts in relationship could be useful to describe patient conditions more precisely. Similarly, loss of control has been described as "independence/dependency", "clear decision-making/autonomy", "uncertainty", or overall "control" in previous studies [2, 4, 11, 16, 19, 20]. This study identified three specific areas influenced by sense of control, namely, physical control (independence), cognitive control (autonomy), and control over the future (uncertainty). We believe that this classification could be useful in understanding which area is the chief component of a specific patient's distress related to loss of control.

The category of "loss of continuity" includes three areas: role, enjoyable activity, and being oneself. Although this corresponds to "continuity", "role", "contribution", "loss of previous identity", "loss of self", and "cosmetic loneliness" described in previous studies [4, 11, 14, 16, 20], we think that this category might include heterogeneous concepts, compared with other categories. Further studies should clarify whether this category is the best description for this type of existential suffering. On the other hand, the remaining categories coincide well with those described in previous studies: burden on others refers to "burden on others" and "troubling others" [4, 11, 16, 19]; uncompleted life task corresponds to "completion", "legacy", "generatavity", and "unfinished business" [4, 16, 20]; hope/hopelessness corresponds to "hope" [4, 15, 16]; and acceptance/preparation corresponds to "acceptance", "wishes for health", "preparation", "death anxiety", "life after death", "imagery of death", "parting from life", "fears", and "death and dying" [4, 11, 15, 16, 20, 21].

The conceptualization of existential concerns suggests effective therapeutic strategies for each specific situation, in addition to general psychoexistential care including a support-expressive approach, person-centered care, and intensive symptom control. Table 2 shows the specific interventions we believe would be effective in alleviating each existential distress. The bases of these proposed care strategies are a systematic review of the Japanese and English literature, an opinion survey of Japanese experts, and discussion among the authors [10, 17]. These care strategies are similar to the practical model of Block [1] and Chochinov [4]. Clinical studies of the usefulness of these recommended care strategies are promising.

Despite its strengths in obtaining a non-selected sample from multiple centers, this study had several limitations. First, as the nurses recorded all data as a part of daily practice, some expressions about existential concerns that nurses could not identify might not have been recorded. Especially, we found no categories related to meaning, calm and peaceful state of mind, or guilt, which have frequently been identified as expressions of existential distress in terminally ill patients [2, 11, 16, 21], and the prevalence of each concern was generally low. This suggests a significant observer bias in identifying existential concerns that might not be always voluntarily reported by patients. Second, as all study populations were patients admitted to palliative care units, the findings could not be straightforwardly applied to other populations. Finally, the small sample size makes generalization of the findings difficult.

In conclusion, existential concerns of Japanese terminally ill cancer patients were categorized as relationship-related concerns, loss of control, burden on others, loss of continuity, uncompleted life task, hope/hopelessness, and acceptance/preparation. This classification can contribute to the development of effective therapeutic interventions to alleviate existential distress.

Table 2 Proposed care strategies for specific existential distress

	Specific care strategies
Relationship-related distress	
Isolation/lack of support	Help patients and family to share feelings and time
Concerns about family preparation	Facilitate family grief, support patients to complete life tasks for family
Conflicts in relationship	Identify practical problems and facilitate the resolution
Loss of control	
Physical control (dependency)	Maintain function by rehabilitation and orthotics; facilitate self-care and enhance cognitive control
Cognitive control	Minimize sedative medications; treat cognitive impairment; facilitate "letting-go"
Control over future (uncertainty)	Educate on predicted course; focus on emotional control, not what happens in future; facilitate "letting-go"
Burden on others	Help patients and family share feelings and discuss reality; support patient value
Loss of continuity (role, enjoyable activity, or being oneself)	Preserve achievable role/activity; explore a new role/activity; facilitate review of past accomplishments
Uncompleted life task	Help patients to complete life tasks
Hopelessness	Establish achievable goal; explore expectations after death
Acceptance/preparation	Support patients to receive available treatments and second opinion; support patient coping style; religious counseling

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MASCC

Multinational Association of Supportive Care in Cancer

MASCC BOARD OF DIRECTOR ELECTIONS TO TAKE PLACE IN MARCH/APRIL 2004

The MASCC Board of Directors elections will take place this spring. All currently paid members of MASCC/ISOO will be eligible to vote for nine open Board positions. Members having an e-mail address will receive instructions and a link to the ballot by e-mail. Those who do not have an e-mail address will receive ballots by hard mail.

Douglas Peterson, DMD, Ph.D, chair of the Nominating Committee notes, "the Nominating Committee has been working for several months to define the process, receive and review recommendations, and compile a slate of candidates. We are very pleased with the quality of the candidates and the number of recommendations we received from the membership."

Look in this column next month for the final slate.

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がん患者と対症療法

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チームケアにおける医師の役割と主張

Key Words
コミュニケーション,
緩和ケア病棟,
緩和ケア医,
チームケア,
傾聴

本家好文 県立広島病院緩和ケア科部長

緩和ケア病棟における医師の重要な役割は，まず緩和医療を適切に提供して痛みなどの身体的苦痛を取り除くことである。また患者や家族が病状に関して納得できるような話し合いの場をもつことも大切である。そのうえでその後の療養の方法を自分自身で選択できるように援助することも重要な役割といえる。

医師は従来のような医師主導の医療を提供するのではなく，よい意味でのリーダーシップを発揮しながら，チームメンバーの１人として患者や家族のQOLを向上させることを共通目標にする必要がある。そのためには他のメンバーの意見を十分に聴くことに努めながらコミュニケーションをとることを尊重する必要がある。

はじめに

1990年に緩和ケア病棟施設基準が設置され，一定の基準を満たした施設で「緩和ケア病棟入院料」に基づいた定額制による運用がはじまった。その後，緩和ケア病棟入院料が徐々に増額されたことも手伝って，緩和ケア病棟の施設数と病床数は1998年頃から急速に増加し，2004年３月１日時点では全国の承認施設数は126，病床数は2,408床となっている。1990年の発足当初に比べると，施設数で約25倍，病床数で約20倍になる[1]。

わが国の緩和ケアは緩和ケア病棟を中心に広がりをみせてきたが，施設をつくることが先行しすぎてスタッフの教育などが遅れた結果，緩和ケアの理念を理解したり緩和医療技術を習得しないままで見切りスタートを切る施設も見受けられる。ケアを担うスタッフの教育や研修が十分実施できていないことは，ケアの質を維持するうえで大きな問題となっている。

特に医師については，人材の確保が困難な状況が続いている。緩和ケア病棟に勤務している医師の中には，必ずしも本人の意向で緩和ケアに従事していない医師がいることも事実である。本稿では緩和ケア病棟で働く医師の役割や，抱えている

Doctor's role and duty at team care
Yoshifumi Honke