The incidence and prevalence of pancreatic neuroendocrine tumors are increasing[1-3]; these tumors represent approximately 1.3% of all cases of pancreatic cancer in incidence and 10% of cases in prevalence.[1-3] Pancreatic neuroendocrine tumors are frequently diagnosed at a late stage, with approximately 65% of patients presenting with unresectable or metastatic disease; as a result, these patients have a poor prognosis. The median survival time for patients with distant metastatic disease is 24 months,[2] and limited treatment options are available for this population.

Streptozocin is the only approved therapy for pancreatic neuroendocrine tumors in the United States; however, the role of chemotherapy in advanced cases continues to be debated.[3-12] The criteria that were used to determine the outcome measures in many earlier trials are considered unacceptable today, and a substantial number of adverse events were seen with regimens that showed improved response rates.[3,10,13,14] Large, prospective, randomized trials that use validated criteria are therefore required to show the value of promising new treatment regimens for advanced pancreatic neuroendocrine tumors. A recent prospective study (reported by Raymond et al. elsewhere in this issue of the *Journal*) shows that sunitinib has antitumor activity.[15]

Everolimus (Afinitor, Novartis Pharmaceuticals) has recently shown promising antitumor activity in two phase 2 studies involving patients with pancreatic neuroendocrine tumors.[3,16] Everolimus inhibits mammalian target of rapamycin (mTOR), a serine–threonine kinase that stimulates cell growth, proliferation, and angiogenesis.[3,16,17] Autocrine activation of the mTOR signaling pathway, mediated through insulin-like growth factor 1, has been implicated in the proliferation of pancreatic neuroendocrine tumor cells.[18] Consistent with this observation is the finding that inhibition of mTOR has a significant antiproliferative effect on pancreatic neuroendocrine tumor cell lines.[19,20]

The RAD001 in Advanced Neuroendocrine Tumors, third trial (RADIANT-3) study was conducted to determine whether everolimus, at a dose of 10 mg per day, as compared with placebo, would prolong progression-free survival among patients with advanced pancreatic neuroendocrine tumors.

METHODS

PATIENTS

Patients were eligible to be included in the study if they were 18 years of age or older and had low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumors and radiologic documentation of disease progression (an unequivocal increase in the size of tumors) in the 12 months preceding randomization. Prior antineoplastic therapy was not an exclusion criterion. Other key eligibility criteria included the presence of measurable disease, as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (see the Supplementary Appendix, available with the full text of this article at NEJM.org)[21]; a World Health Organization (WHO) performance status of 2 or less (with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction; 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work; and 2 indicating that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities)[22]; adequate bone marrow, renal, and hepatic function; and adequately controlled lipid and glucose concentrations. Patients were ineligible if they had undergone hepatic-artery embolization within 6 months before enrollment (within 1 month if there were other sites of measurable disease) or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrollment, had any severe or uncontrolled medical conditions, had received prior therapy with an mTOR inhibitor, or were receiving long-term treatment with glucocorticoids or other immunosuppressive agents.

STUDY OVERSIGHT

The protocol was approved by the institutional review board or ethics committee at each participating center, and the study was conducted in accordance with Good Clinical Practice principles and applicable local regulations. All patients provided written informed consent.

The study was designed by the academic investigators and by representatives of the sponsor,

Novartis Oncology. The data were collected with the use of the sponsor's data management systems and were analyzed by the sponsor's statistical team. All the authors contributed to the interpretation of data and the subsequent writing, reviewing, and amending of the manuscript; the first draft of the manuscript was prepared by the first author and by a medical writer employed by Novartis Oncology. The protocol, including the statistical analysis plan, is available at NEJM.org. All the authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan.

STUDY DESIGN AND TREATMENT

In this international, multicenter, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus, at a dose of 10 mg once daily, or matching placebo, both in conjunction with best supportive care. Patients were stratified according to status with respect to prior chemotherapy (receipt vs. no receipt) and according to WHO performance status (0 vs. 1 or 2) at baseline.

Treatment continued until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent. The study-group assignments were concealed from the investigators, but disclosure was permitted if an investigator determined that the criteria for disease progression according to RECIST had been met and if there was an intention to switch the patient to open-label therapy. Patients who had been assigned to placebo initially could then switch to open-label everolimus. This element of the study design was incorporated to address both ethical and recruitment considerations, given that the trial involved patients with a rare disease. We recognized the potential influence of this aspect of the study design on the analysis of the end point of overall survival.

Doses were delayed or reduced if patients had clinically significant adverse events that were considered to be related to the study treatment, according to an algorithm described in the protocol. In such cases, two reductions in the dose of the study drug were permitted: an initial reduction to 5 mg daily and a subsequent reduction to 5 mg every other day.

EFFICACY AND SAFETY ASSESSMENTS

The primary end point was progression-free survival, documented by the local investigator according to RECIST and defined as the time from randomization to the first documentation of disease progression or death from any cause. If the disease had not progressed and the patient had not died as of the cutoff date for the analysis, data for progression-free survival were censored at the time of the last adequate tumor assessment — which was defined as the last assessment of overall lesion response that showed complete response, partial response, or stable disease — before the cutoff date or the date of initiation of other anticancer therapy.[23] In the primary analysis, data for progression-free survival were censored at the time of the last adequate tumor assessment if an event occurred after two or more missing tumor assessments. Data for patients without any valid post-baseline tumor assessment were censored on day 1 (the date of randomization). Secondary end points included the confirmed objective response rate (according to RECIST, version 1.0), the duration of response, overall survival, and safety.

All randomly assigned patients were assessed for efficacy (intention-to-treat analysis). Tumor measurements (assessed by triphasic computed tomography or magnetic resonance imaging) were performed at baseline and were repeated every 12 weeks. Scans were reviewed at the local site and centrally. In cases of a discrepancy between the local investigator's assessment and the radiologic assessment at the central location with respect to the determination of progression-free survival, adjudication was performed by an independent central adjudication committee comprising a board-certified radiologist and an oncologist, both of whom had extensive experience with neuroendocrine tumors. The central adjudication committee, whose members were unaware of the patients' study-group assignments and of the source of the data (local or central), selected the assessment that in their expert opinion reflected the more accurate evaluation.

All patients who received at least one dose of the study drug and had at least one follow-up assessment were evaluated for safety. Safety assessments consisted of the monitoring and recording of all adverse events, regular monitoring of hematologic and clinical biochemical levels (lab-

oratory evaluations) and vital signs, and physical examinations every 4 weeks. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

The estimation of the sample size was based on the ability to detect a clinically meaningful improvement in the primary end point, which was defined as a 33% reduction in the risk of disease progression or death (a hazard ratio for progression or death of 0.67), corresponding to a 50% prolongation in median progression-free survival, from 6 months with placebo to 9 months with everolimus. We estimated that with a total of 282 progression-free survival events (i.e., disease progression or death), the study would have 92.6% power to detect a clinically meaningful improvement, with the use of an unstratified log-rank test, at a one-sided significance level of 2.5%. Taking into account the estimated rate of patient accrual and a 10% loss of the study population to follow-up, we estimated that we would have to enroll 392 patients to observe the required number of events.

Progression-free and overall survival were analyzed with the use of Kaplan–Meier methods; study groups were compared with the use of a log-rank test, stratified according to prior receipt or no prior receipt of chemotherapy and WHO performance status, and the hazard ratio was estimated with the use of a stratified Cox proportional-hazards model.

RESULTS

PATIENTS AND TREATMENT

Between July 2007 and May 2009, a total of 410 patients from 82 centers in 18 countries worldwide who had advanced pancreatic neuroendocrine tumors were randomly assigned to everolimus (207 patients) or placebo (203 patients) (see the figure in the Supplementary Appendix). The baseline demographic and clinical characteristics of the patients were well balanced between the two groups (Table 1). More than 80% of the patients had well-differentiated disease, more than 90% had metastases in the liver, and approximately 60% had received a diagnosis of pancreatic neuroendocrine tumor more than 2 years before entering the study. A total of 24% of the patients had gastrinoma, glucagonoma, VIPoma, insulinoma, or somatostatinoma. The two groups were similar with respect to prior receipt of radiother-

Table 1. Demographic and Baseline Clinical Characteristics of the Patients.

Characteristic	Everolimus (N=207)	Placebo (N=203)
Age — yr		
Median	58	57
Range	23–87	20–82
Sex — no. (%)		
Male	110 (53)	117 (58)
Female	97 (47)	86 (42)
WHO performance status — no. (%)		
0	139 (67)	133 (66)
1	62 (30)	64 (32)
2	6 (3)	6 (3)
Histologic status of tumor — no. (%)		
Well differentiated	170 (82)	171 (84)
Moderately differentiated	35 (17)	30 (15)
Unknown	2 (1)	2 (1)
Time from initial diagnosis — no. (%)		
≤6 mo	24 (12)	33 (16)
>6 mo to ≤2 yr	65 (31)	43 (21)
>2 yr to ≤5 yr	54 (26)	81 (40)
>5 yr	64 (31)	46 (23)
Time from disease progression to randomization — no. (%)		
≤1 mo	73 (35)	61 (30)
>1 mo to ≤2 mo	43 (21)	53 (26)
>2 mo to ≤3 mo	30 (14)	29 (14)
>3 mo to ≤12 mo	58 (28)	54 (27)
>12 mo	3 (1)	1 (<1)
No. of disease sites — no. of patients (%)		
1	51 (25)	62 (31)
2	85 (41)	64 (32)
≥3	70 (34)	77 (38)
Organ involved — no. (%)		
Liver	190 (92)	187 (92)
Pancreas	92 (44)	84 (41)
Lymph nodes	68 (33)	73 (36)
Lung	28 (14)	30 (15)
Bone	13 (6)	29 (14)

Table 2. Progression-free Survival.

Variable	Everolimus (N=207)	Placebo (N=203)	Difference	Hazard Ratio for Disease Progression or Death with Everolimus (95% CI)	P Value
Assessment by local investigator					
Progression-free survival events — no. (%)*	109 (53)	165 (81)			
Censored data — no. (%)	98 (47)	38 (19)			
Median progression-free survival — mo	11.0	4.6	6.4	0.35 (0.27–0.45)	<0.001
Review by central adjudication committee					
Progression-free survival events — no. (%)*	95 (46)	142 (70)			
Censored data — no. (%)	112 (54)	61 (30)			
Median progression-free survival — mo	11.4	5.4	6.0	0.34 (0.26–0.44)	<0.001

* Progression-free survival events include disease progression and death.

apy (23% of patients in the everolimus group and 20% in the placebo group), chemotherapy (50% in both groups), and somatostatin analogue therapy (49% in the everolimus group and 50% in the placebo group). Best supportive care included the use of somatostatin analogue therapy in approximately 40% of the patients.

With a median follow-up period of 17 months, the median duration of treatment with everolimus was 8.79 months (range, 0.25 to 27.47), as compared with 3.74 months (range, 0.01 to 37.79) with placebo. A total of 31% of the patients in the everolimus group, as compared with 11% in the placebo group, were administered treatment for a minimum of 12 months. The mean relative dose intensity (the ratio of administered doses to planned doses) was 0.86 in the everolimus group and 0.97 in the placebo group. Dose adjustments (reductions or temporary interruptions) were required by 59% of the patients receiving everolimus and 28% of the patients receiving placebo.

At the time the analysis was performed for this article, treatment was ongoing for 32% of the patients in the everolimus group and 13% of the patients in the placebo group; the primary reasons for discontinuation of treatment included disease progression (in 44% of patients in the everolimus group vs. 80% in the placebo group), adverse events (17% vs. 3%), withdrawal of consent (2% in both groups), and death (2% vs. 1%).

EFFICACY

The median progression-free survival (the primary end point), as assessed by the local investigators, was 11.0 months (95% confidence interval [CI], 8.4 to 13.9) in the everolimus group, as compared with 4.6 months (95% CI, 3.1 to 5.4) in the placebo group, representing a 65% reduction in the estimated risk of progression (hazard ratio for disease progression or death with everolimus, 0.35; 95% CI, 0.27 to 0.45; P<0.001) (Table 2 and Fig. 1A). The estimated proportion of patients who were alive and progression-free at 18 months was 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo, indicating that a sizable proportion of patients derived a prolonged benefit with everolimus.

The findings of the independent adjudicated central assessment of median progression-free survival were consistent with those of the assessment by local investigators. The median progression-free survival according to the central assessment was 11.4 months (95% CI, 10.8 to 14.8) with everolimus, as compared with 5.4 months (95% CI, 4.3 to 5.6) with placebo (hazard ratio for disease progression or death with everolimus, 0.34; 95% CI, 0.26 to 0.44; P<0.001) (Table 2 and Fig. 1B).

Prespecified subgroup analyses indicated that the benefit was maintained across subgroups. A benefit with everolimus was evident irrespective of status with respect to prior chemotherapy (receipt or no receipt), WHO performance status, age, sex, race, geographic region, status with respect to prior somatostatin analogue therapy (receipt or no receipt), and tumor grade (Fig. 1C).

Everolimus was associated with a superior response profile, as assessed according to RECIST (P<0.001 with the use of a two-sided Mann–Whit-

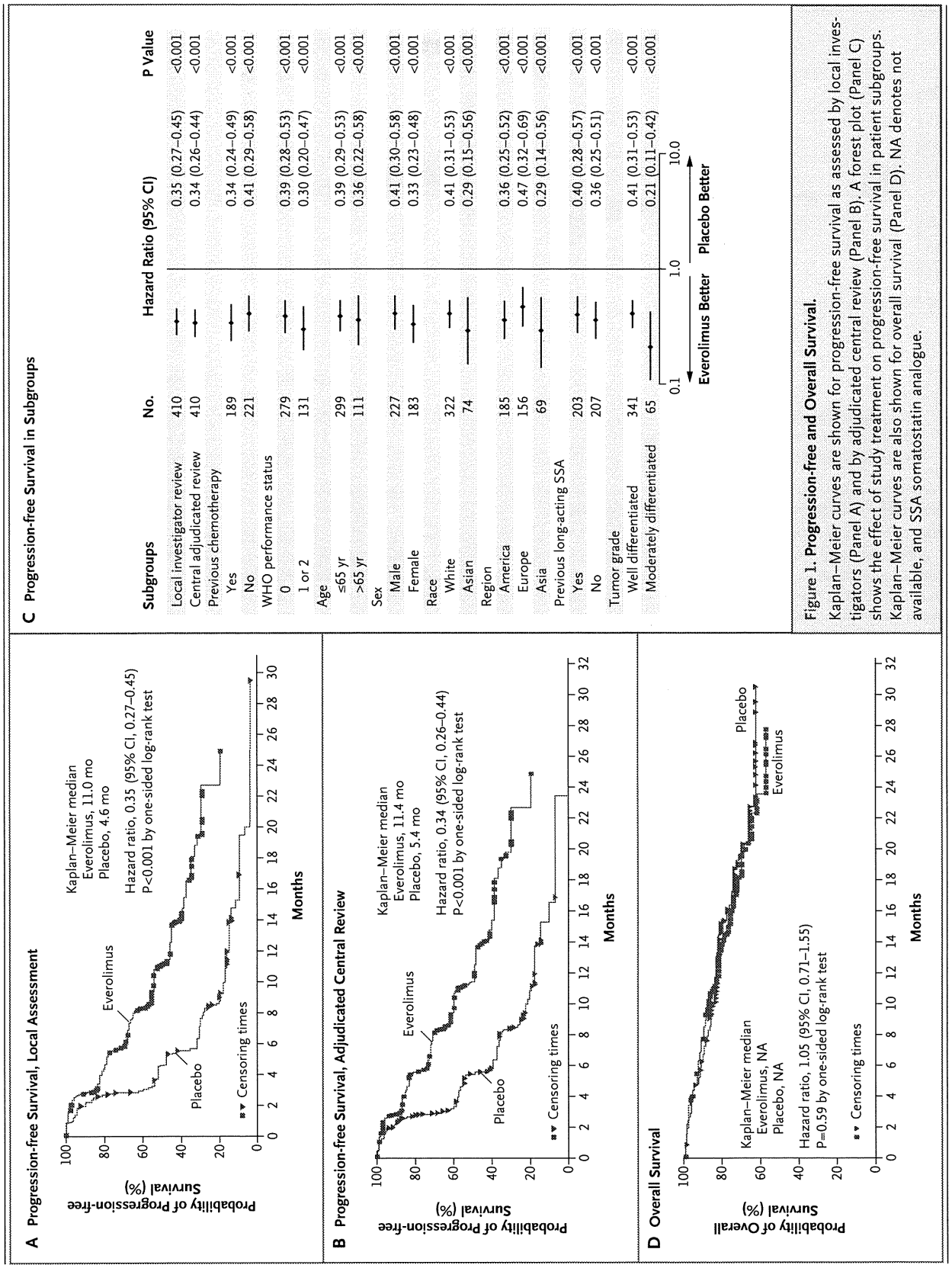
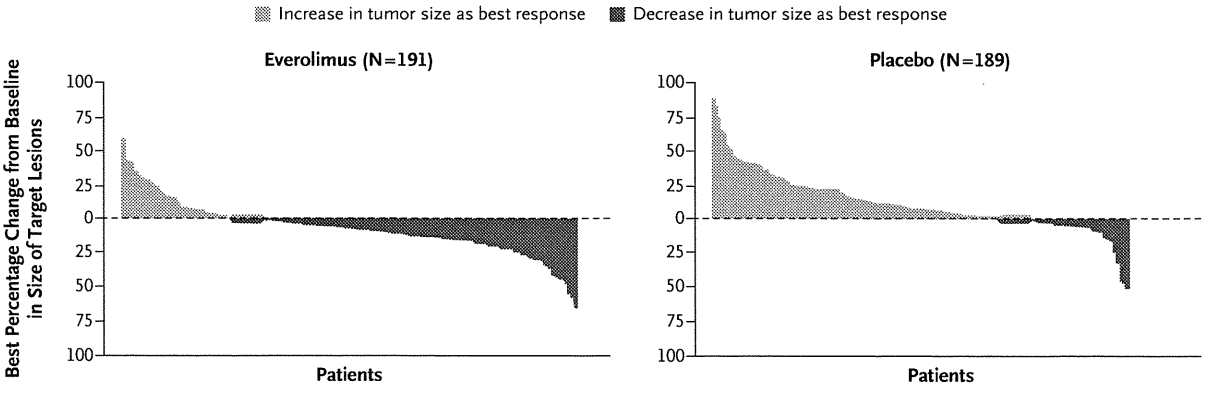


Figure 1. **Progression-free and Overall Survival.**
Kaplan–Meier curves are shown for progression-free survival as assessed by local investigators (Panel A) and by adjudicated central review (Panel B). A forest plot (Panel C) shows the effect of study treatment on progression-free survival in patient subgroups. Kaplan–Meier curves are also shown for overall survival (Panel D). NA denotes not available, and SSA somatostatin analogue.



	Everolimus	Placebo
	no. (%)	
Decrease in size of target lesions from baseline	123 (64.4)	39 (20.6)
No change in size of target lesions from baseline	11 (5.8)	10 (5.3)
Increase in size of target lesions from baseline	43 (22.5)	112 (59.3)

Figure 2. Percentage Change from Baseline in Size of Target Lesion.

The plot shows the best percentage change from baseline in the size of the target lesion (i.e., the best response in each patient) in the everolimus group (left) and the placebo group (right). Data on 30 patients with lesions that could be evaluated in the everolimus group and 42 in the placebo group were not included in the analysis for the following reasons: 14 in the everolimus group (7.3%) and 28 in the placebo group (14.8%) showed a change in the available target lesion that contradicted the overall response of progressive disease; 1 patient in the everolimus group (0.5%) showed a change in the available target lesion, but the overall response was unknown; and the change in the target lesion could not be assessed in 15 patients in the everolimus group (7.9%) and 14 in the placebo group (7.4%).

ney U test). Confirmed objective tumor responses as assessed by local investigators (all partial responses) were observed in 10 patients receiving everolimus (5%) as compared with 4 patients receiving placebo (2%). Thus, the benefit from everolimus with respect to progression-free survival was seen primarily in the stabilization of disease or minor tumor shrinkage and in the lower incidence of progressive disease. Stable disease was evident in the case of 73% of the patients in the everolimus group as compared with 51% in the placebo group. Progressive disease as the best outcome occurred in 14% of the patients receiving everolimus and 42% of the patients receiving placebo. A total of 64% of the patients receiving everolimus, as compared with 21% receiving placebo, had some degree of tumor shrinkage (Fig. 2).

Of the 203 patients initially assigned to receive placebo, 148 (73%) crossed over to open-label everolimus, thus confounding the detection of a treatment-related survival benefit. Median overall survival was not reached at the time of this analysis, and no significant difference between the groups was observed (hazard ratio for death with everolimus, 1.05; 95% CI, 0.71 to 1.55; P=0.59) (Fig. 1D). The final analysis of overall survival will be performed once approximately 250 deaths have occurred.

SAFETY

Our findings with respect to safety were consistent with the known safety profile of everolimus, and most adverse events were grade 1 or 2. The most common drug-related adverse events occurring with a frequency of at least 10% are listed in Table 3. A total of 12 patients in the everolimus group (6%) and 4 in the placebo group (2%) died while receiving the study drug. Of these 16 deaths, 8 (5 in the everolimus group and 3 in the placebo group) were attributed to the underlying cancer or disease progression. The remaining 8 cases (7 in the everolimus group and 1 in the placebo group) were attributed to adverse events; of these, 1 in the everolimus group was related to the study drug.

The most common adverse events were stomatitis (in 64% of the patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs.

14%), and infections (23% vs. 6%). Infections, as well as pneumonitis (which occurred in 12% of the patients in the everolimus group vs. 0% in the placebo group) and interstitial lung disease (2% vs. 0%), represented some of the most important clinical concerns and were primarily grade 1 or 2. The most common grade 3 or 4 drug-related adverse events were anemia, hyperglycemia, stomatitis, thrombocytopenia, diarrhea, hypophosphatemia, and neutropenia. Antibiotics were routinely prescribed for patients with infections. Glucocorticoids were administered to six of the seven patients with grade 3 or 4 noninfectious pneumonitis or interstitial lung disease; however, only 5 (2%) of these events were considered to be drug-related (Table 3). Atypical infections such as pulmonary tuberculosis, bronchopulmonary aspergillosis, and reactivation of hepatitis B (each of which occurred in one patient) were also observed in association with everolimus therapy.

The death from acute respiratory distress syndrome of one patient with insulinoma in the everolimus group (who was receiving glucocorticoid therapy) was considered to be treatment-related. Adverse events related to the study drug led to discontinuation of treatment in the case of 13% of the patients receiving everolimus (with pneumonitis, fatigue, and interstitial lung disease cited as the most common reasons) and 2% of the patients in the placebo group (as a result of cardiac failure, diarrhea, confusion and depressed level of consciousness, and elevated alanine aminotransferase concentrations). The most common drug-related adverse events necessitating dose adjustment were stomatitis (in 10% of the patients in the everolimus group vs. <1% in the placebo group), pneumonitis (7% vs. 0%), thrombocytopenia (7% vs. 0%), diarrhea (4% vs. 0%), and anemia (3% vs. 0%).

Table 3. Drug-Related Adverse Events Occurring in at Least 10% of Patients.

Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

* Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.
† All types of infections are included.
‡ Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

DISCUSSION

In this trial, we compared everolimus with placebo in patients with advanced pancreatic neuroendocrine tumors in whom the disease had progressed within the previous 12 months. The majority of patients had received prior treatment with chemotherapy, radiotherapy, somatostatin analogue therapy, or some combination of those therapies. Everolimus, as compared with placebo, was associated with a 6.4-month prolongation of the median progression-free survival (an increase by a factor of 2.4). The patients in our study, who otherwise had a poor prognosis, had a 65% reduction in the relative risk of progression with everolimus therapy as compared with placebo ($P<0.001$). This study confirmed the prolonged progression-free survival that had been observed with everolimus in earlier phase 2 studies.[3,16]

Although the molecular pathogenesis of sporadic pancreatic neuroendocrine tumors is unknown, several genetic cancer syndromes involving the mTOR pathway, including tuberous sclerosis, neurofibromatosis, and von Hippel–Lindau disease, are linked to the development of pancreatic

neuroendocrine tumors.[24] In sporadic pancreatic neuroendocrine tumors, down-regulation of tuberin (TSC2) and phosphatase and tensin homologue (PTEN) leads to dysregulation of the mTOR pathway. Low TSC2 and PTEN are linked to progression of the cancer, an increased rate of proliferation (as assessed by Ki 67 labeling), and shortened progression-free and overall survival.[20] In a study of paired biopsy specimens, treatment with everolimus reduced tumor proliferation in neuroendocrine tumors, as evidenced by a decreasing percentage of cells with Ki 67 labeling.[16] The magnitude of the clinical benefit observed in our study confirms the importance of the mTOR pathway in pancreatic neuroendocrine tumors.

Sunitinib, an oral inhibitor of a number of tyrosine kinases (but not an inhibitor of mTOR), also shows activity against advanced pancreatic neuroendocrine tumors.[15] It is not yet clear whether sunitinib and everolimus can be combined and, if so, whether antitumor activity would be further increased with combined treatment.

We have previously shown that everolimus can be safely administered to patients with neuroendocrine tumors either with or without concurrent octreotide long-acting release (LAR) therapy.[3] The safety profile of everolimus in the current study was consistent with that in previous phase 2 studies. Despite a significantly longer duration of exposure in the population of patients with pancreatic neuroendocrine tumors, the rate of adverse events was similar to that in phase 3 trials involving patients with renal-cell carcinoma.[25] The most common drug-related adverse event in our trial was stomatitis or aphthous ulceration, characterized by sporadic occurrences of discrete white ulcerations that frequently appeared and resolved during treatment. Everolimus therapy can also be associated with mild lymphopenia and neutropenia. Although in our trial, infections were more common among patients receiving everolimus than among those receiving placebo, grade 3 or 4 drug-related infections occurred in only 2% of the patients in the everolimus group. The most commonly reported infections were mild upper respiratory infections. Adverse events were generally manageable, as evidenced by the low rate of discontinuation of treatment. Noninfectious pneumonitis and interstitial lung disease, potentially serious adverse events associated with sirolimus (previously called rapamycin) derivatives, were also observed, but these events can be effectively managed according to existing treatment guidelines.

In summary, our study shows that everolimus, as compared with placebo, improves progression-free survival in patients with advanced pancreatic neuroendocrine tumors. The adverse events seen with everolimus were mainly grade 1 and 2 events, thus allowing for long-term daily administration.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Phase II study of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer

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Abstract
Purpose The primary objective of this study was to assess the efficacy and safety of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer.
Methods Patients with histologically or cytologically proven, advanced pancreatic cancer who had received first-line chemotherapy with gemcitabine were eligible for this study. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for 28 days, followed by 14 days' rest. Treatment was repeated every 6 weeks until disease progression.
Results Twenty-one patients were enrolled in this study. Grade 3 and 4 toxicities included anorexia in 14% of the patients, abdominal pain in 4.8% and infection without neutropenia in 4.8%. S-1 was discontinued in two patients because of toxicity. Of the 21 eligible patients, 2 (9.5%) achieved a partial response and 9 (43%) had stable disease. A marked decrease (≥50%) in tumor marker (CA19-9) was observed in 5 (28%) of the 18 evaluable patients. The median progression-free survival and the median survival time from the first day of S-1 therapy were 4.1 months (95% CI, 1.3–6.9 months) and 6.3 months (95% CI, 3.6–8.9 months), respectively.
Conclusions Second-line chemotherapy with S-1 was tolerated with acceptable toxicity and resulted in a relatively high disease control rate in patients with gemcitabine-resistant advanced pancreatic cancer. As an oral agent, S-1 may be a feasible treatment option for this patient population.

Keywords Pancreatic cancer · S-1 · Second-line therapy · Phase II study

Introduction

Pancreatic cancer is one of the most prevalent gastrointestinal tumors and its prognosis is extremely poor. A previous randomized trial of gemcitabine in patients with advanced pancreatic cancer has shown this drug is superior to 5-fluorouracil (5-FU) in terms of overall survival and clinical benefit [1], and treatment with gemcitabine alone has been accepted as the only approved therapy for unresectable pancreatic cancer. In an effort to improve therapeutic efficacy, various studies have investigated gemcitabine-based combination regimens. However, most of those studies have found a low impact on survival, and gemcitabine monotherapy is still considered as the standard treatment for this disease.

There is no accepted second-line treatment for advanced pancreatic cancer after gemcitabine failure. Although several studies have shown the efficacy and safety of second-line chemotherapy in a selected patient population [2], second-line strategies are often hard to implement due to the poor condition and prognosis of the patients. Thus,

This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. All study participants provided written informed consent. This manuscript has not been published and is not under consideration for publication elsewhere.

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there is an urgent need to develop effective therapies for tumors refractory to treatment with gemcitabine.

S-1 is an oral fluorinated pyrimidine, which was designed to improve the antitumor activity of 5-FU while reducing gastrointestinal toxicity, based on a hypothetical biochemical modulation of 5-FU. S-1 contains tegafur, 5-chloro-2, 4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a molar ratio of 1:0.4:1 [3]. Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU by hepatic microsomal enzymes. Gimeracil inhibits the degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD) and it is 180 times more potent than uracil, a DPD inhibitor included in UFT; thus, an efficacious concentration of 5-FU is maintained both in plasma and tumor tissues [4]. Oteracil is a competitive inhibitor of orotate phosphoribosyltransferase that inhibits phosphorylation of 5-FU in the gastrointestinal tract. Because oteracil preferentially acts in the gastrointestinal tract after oral administration, it reduces the gastrointestinal toxicity associated with 5-FU [5].

S-1 has shown favorable antitumor activity in several phase II studies in patients with various solid tumors [6–9], and a recent phase II study of S-1 in patients with metastatic pancreatic cancer yielded a good response rate of 37.5% and median survival of 9.2 months [10]. Furthermore, recent studies of combination chemotherapy with S-1 and gemcitabine for metastatic pancreatic cancer yielded a promising response rate of 44–48% and a median survival time of 10.1–12.5 months [11, 12]. Based on currently available data, S-1 seems to have significant activity against advanced pancreatic cancer; thus, we selected S-1 to treat patients with gemcitabine-resistant pancreatic cancer.

Patients and methods

Eligibility

Patients with histologically or cytologically proven, advanced adenocarcinoma of the pancreas who had received first-line chemotherapy with gemcitabine were eligible for this study. Participants were required to be at least 20 years old and to have an Eastern Cooperative Oncology Group performance status of 2 or less and adequate organ function defined by the following parameters: leukocytes $\geq$3,500/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dL, normal serum creatinine, a serum glutamic oxaloacetic transaminase (GOT) <150 IU/L, a serum glutamic pyruvic transaminase (GPT) <150 IU/L and serum bilirubin $\leq$2.0 mg/dL.

Patients were excluded if they had interstitial pneumonitis, active inflammatory bowel disease, active infection, mental disorder, or other severe concurrent disease. Patients with other malignancies and pregnant or lactating women were also excluded.

This study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000. The protocol was approved by the Institutional Review Board of Chiba University Graduate School of Medicine. Written informed consent was obtained from all patients before their inclusion into the study.

Treatment

S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily after a meal for 28 consecutive days, and the course was repeated after 14 days' rest, until disease progression or unacceptable toxicities. Three initial doses were established according to the body surface area (BAS) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA < 1.50 m^2, 100 mg/day; 1.50 m^2 $\leq$ BSA, 120 mg/day.

Dose modification

S-1 was temporally discontinued when any of the following conditions were encountered: leukocytes <2,000/mm^3, neutrophils <1,000/mm^3, hemoglobin <8.0 g/dL, platelets <75,000/mm^3, serum GOT/GPT $\geq$ 150 IU/L, serum total bilirubin $\geq$3.0 mg/dL, serum creatinine $\geq$1.5 mg/dL, or when grade 3 non-hematological toxicity was observed. Administration was resumed when the toxicity resolved. When grade 4 hematological toxicity or grade 3 or greater non-hematological toxicity occurred, the dose of S-1 was reduced by 20 mg/day. If it was difficult to administer S-1 for 28 consecutive days because of tumor-related symptoms or non-severe toxicity, which did not meet the dose reduction criteria (e.g. grade 2 anorexia or nausea), a regimen consisting of S-1 administration for 14 consecutive days followed by 7 days' rest (2-week administration regimen) was permitted, since this regimen was recently reported to be more feasible and did not require a change in dose intensity, when compared to the standard 4-week administration regimen (28 consecutive days followed by 14 days' rest) [13].

Follow-up evaluation

Pretreatment evaluation included a medical history and physical examination, complete blood count and biochemistry test, a chest radiogram, and CT of the abdomen and pelvis. Complete blood counts and serum biochemistry tests were performed weekly during the first course of S-1 and every other week after the second course. Biochemistry

tests included standard serum tests such as total protein, albumin, bilirubin, GOT, GPT, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, creatinine, and C-reactive protein. Treatment-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Follow-up CT was performed every 2 months to assess objective tumor response according to the Response Evaluation Criteria in Solid Tumors. Serum CA 19-9 levels were measured monthly using a commercially available chemiluminescent enzyme immunoassay kit based on the two-step sandwich method (CL-EIA). A value of 39.5 U/mL was defined as the upper normal limit.

Statistics

The primary end-point was the objective response rate (complete response or partial response), with secondary end-points including overall and progression-free survival, disease control rate (complete response, partial response or stable disease), and safety of S-1. The number of patients required for this study was calculated according to the optimal two-stage design. The threshold response rate and expected response rate were 5% and 20%, respectively. The number of patients was 19 (α- and β-error probabilities 0.05 and 0.2). Both survival and tumor response were determined according to the intention-to-treat principle in all enrolled patients. Overall survival and progression-free survival were calculated with the Kaplan–Meier method.

Results

Patient characteristics

From March 2005 to July 2006, 21 patients entered this study. The patients' characteristics are listed in Table 1. All patients had been treated with gemcitabine alone. The median progression-free survival with first-line gemcitabine was 3.2 months. At the time of enrollment, most patients (95%) had evidence of metastatic disease and one patient had locally advanced unresectable disease. Seventy-one percent of the patients had an ECOG performance status of 0 or 1.

A total of 66 cycles were delivered (median, 3; range, 0–13). Based on the dose modification guidelines, the 2-week administration regimen was adopted in ten patients (48%).

Toxicity

All treated patients ($n = 21$) were assessed for toxicities. The toxicities observed during treatment are listed in Table 2. Generally, hematological toxicity was mild, and no grade 3 or higher toxicity was observed. As for non-hematological toxicity, grade 3 anorexia (14%), grade 3 abdominal pain (4.8%), and grade 3 infection (4.8%) was experienced. One patient developed duodenal bleeding 54 days after the beginning of S-1 treatment requiring embolization under angiography. This was considered to be tumor bleeding unrelated to the medication. Second-line chemotherapy with S-1 was feasible with acceptable toxicity and no treatment-related deaths occurred.

Table 1 Patient characteristics

Number of patients	21
Gender	
Men	13
Women	8
Age, years	
Median (range)	64 (32–75)
ECOG performance status	
0	4
1	11
2	6
Disease status	
Locally advanced	1
Metastatic	20

ECOG Eastern cooperative oncology group

Table 2 Toxicity ($n = 21$)

Toxicity	No. of patients (%)		
	Grade 1/2	Grade 3	Grade 4
Hematological toxicity			
Leukocytopenia	6 (29)	0	0
Neutropenia	4 (19)	0	0
Anemia	4 (19)	0	0
Thrombocytopenia	7 (33)	0	0
Non-hematological toxicity			
Anorexia	4 (19)	3 (14)	0
Nausea	5 (24)	0	–
Vomiting	2 (9.5)	0	0
Diarrhea	3 (14)	0	0
Stomatitis	2 (9.5)	0	0
Elevation of GOT/GPT	5 (24)	0	0
Elevation of creatinine	1 (4.8)	0	0
Hyperbilirubinemia	1 (4.8)		
Abdominal pain	2 (9.5)	1 (4.8)	0
Infection without neutropenia	2 (9.5)	1 (4.8)	0

GOT glutamic oxaloacetic transaminase, *GPT* glutamic pyruvic transaminase

Response and survival

Partial response was achieved in 2 patients, and the disease remained stable in 9, with a response rate of 9.5% (95% CI, 0–22%) and a disease control rate of 52%. Eighteen patients had elevated serum levels of CA 19-9 (median/range, 1998/42-49420 U/mL) without jaundice before treatment. The CA 19-9 level after treatment decreased more than 50% in 5 (28%) of those 18 patients and showed a normal value in 2 (11%).

The median progression-free survival and the median survival time from the first day of S-1 therapy were 4.1 months (95% CI, 1.3–6.9 months) and 6.3 months (95% CI, 3.6–8.9 months), respectively (Fig. 1).

Discussion

There is no accepted second-line treatment for patients with advanced pancreatic cancer who do not respond to treatment with gemcitabine. This study evaluated the use of S-1, a novel oral fluoropyrimidine preparation. As first-line treatment for metastatic pancreatic cancer, S-1 has shown favorable efficacy in clinical trials, but the efficacy and safety of S-1 as a second-line therapy has not been fully evaluated as yet.

In the current study, S-1 showed a modest activity against gemcitabine-resistant pancreatic cancer, yielding a response rate of 9.5%. Although it is difficult to compare our results with those of other studies (Table 3) because of differences in patients' backgrounds, the response rate compares with that (15%) obtained in a previous phase II study of S-1 for gemcitabine-refractory metastatic pancreatic cancer reported by Morizane et al. [14]; and it was equivalent to that of other second-line regimens such as rubitecan (7%) [15], irinotecan (9%) [16], 5FU + celecoxib (12%) [17] or 5FU + paclitaxel (10%) [18]. On the other hand, the disease control rate (52%) of S-1 in the current study was relatively high and comparable to that observed in other active combination regimens for gemcitabine-resistant pancreatic cancer, such as gemcitabine + oxaliplatin (PR 22.6%, SD 38.7%) [19], 5FU + leucovorin + oxaliplatin (PR 23.3%, SD 30%) [20] or irinotecan + raltitrexed (PR 16%, SD 37%) [21]. The median survival time (6.3 months) in this study was also comparable to that (6–6.5 months) reported with other active combination regimens [19–21].

Most patients in the current study had some symptoms related to disease progression or prior chemotherapy at the study entry. It was often difficult to administer S-1 for 28 consecutive days because of tumor-related symptoms or toxicity. To improve therapeutic compliance, the 2-week administration regimen was adopted in ten patients (48%) based on the guidelines for dose modification, since this regimen was recently reported to be more feasible without changing dose intensity compared to the standard treatment schedule [13]. Hematological toxicity of S-1 was mild, and the occurrence of grade 3 or higher hematological toxicity seemed to be lower when compared to other combination regimens. The most common grade 3 non-hematological toxicity of second-line S-1 was anorexia (14%). In the current study, second-line chemotherapy with S-1 was feasible with acceptable toxicity in patients with gemcitabine-resistant advanced pancreatic cancer.

Although the response rate (9.5%) to S-1 in the current study was modest, we consider that the relatively high disease control rate, favorable survival data and toxicity profile may support the use of S-1 as second-line treatment. Furthermore, S-1 has the clinical advantage of being orally administered when compared with infusion regimens. Oral administration of S-1 reduces hospital visits for outpatients and has advantages in terms of quality of life. Considering the extremely poor prognosis of patients with gemcitabine-resistant pancreatic cancer, treatment should be more concerned with their quality of life.

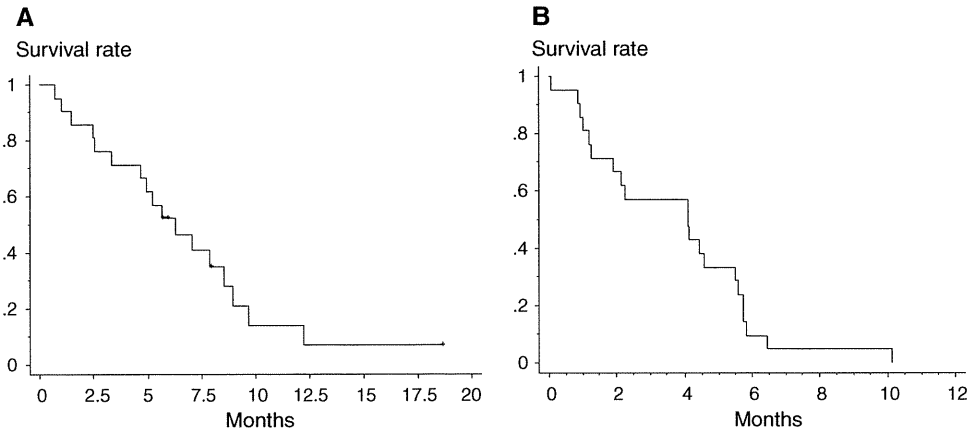

Fig. 1 Overall survival time curve (**a**) and progression-free survival (**b**) from the first day of S-1 therapy

Table 3 Clinical trials in patients with gemcitabine-pretreated advanced pancreatic cancer

Treatment	Number of patients	Response rate (%)	Disease control rate (%)	Progression-free survival	Median overall survival
Oxaliplatin	18	0	16.7	2 months	N/A
Capecitabine	39	0	39	2.3 months	7.6 months
Rubitecan	58	7	23	59 days	92 days
Irinotecan	33	9	48	2 months	6.6 months
S-1	40	15	58	2 months	4.5 months
Oxaliplatin + 5FU + leucovorin	30	23.3	53.3	22 weeks	25 weeks
Xelox (oxaliplatin + capecitabine)	41	2.6	28	9.9 weeks	23 weeks
FDR-GEM + oxaliplatin	33	22.6	61	4.2 months	6 months
5FU + celecoxib	17	12	24	8 weeks	15 weeks
5FU + paclitaxel	28	10	30	2.5 months	7.6 months
Docetaxel + gefitinib	41	2.4	49	1.8 months	4.5 months
Irinotecan + raltitrexed	19	16	53	4 months	6.5 months

FDR fixed dose rate, *N/A* not available

In conclusion, this study has shown that second-line chemotherapy with S-1 is tolerated with acceptable toxicity, and yields a relatively high disease control rate in patients with gemcitabine-resistant pancreatic cancer. As an oral agent, S-1 is a feasible treatment option considering QOL. Our data warrant further studies regarding second-line treatment using S-1 after gemcitabine failure.

Conflicts of interest statement No financial support for this study was provided. The authors report no conflicts of interest.

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CLINICAL INVESTIGATION **Pancreas**

PHASE II STUDY OF ORAL S-1 AND CONCURRENT RADIOTHERAPY IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED PANCREATIC CANCER

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Purpose: S-1 is an oral fluoropyrimidine derivative that has demonstrated favorable antitumor activity in patients with metastatic pancreatic cancer. The aim of this study was to evaluate safety and efficacy of S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer.

Methods and Materials: Patients with histopathologically proven, unresectable, locally advanced pancreatic cancer were eligible. Radiotherapy was delivered in 1.8 Gy daily fractions to a total dose of 50.4 Gy over 5.5 weeks. S-1 was administered orally twice a day at a dose of 80 mg/m^2/day from day 1 to 14 and 22 to 35. Two weeks after the completion of chemoradiotherapy, maintenance chemotherapy with S-1 was administered for 28 days every 6 weeks until progression.

Results: Thirty-four patients were enrolled in this study. The most common Grade 3 toxicities during chemoradiotherapy were anorexia (24%) and nausea (12%). The overall response rate was 41% (95% confidence interval, 25%–58%) and overall disease control rate (partial response plus stable disease) was 97%. More than 50% decrease in serum CA 19-9 was seen in 27 of 29 evaluable patients (93%). The median progression-free survival was 8.7 months. The median overall survival and 1-year survival rate were 16.8 months and 70.6%, respectively.

Conclusions: Oral S-1 and concurrent radiotherapy exerted a promising antitumor activity with acceptable toxicity in patients with locally advanced pancreatic cancer. This combination therapy seems to be an attractive alternative to conventional chemoradiotherapy using 5-fluorouracil infusion. © 2011 Elsevier Inc.

Pancreatic cancer, S-1, Radiotherapy, Phase II study.

INTRODUCTION

Radiotherapy combined with 5-fluorouracil (5-FU) has been the mainstay in the treatment of locally advanced, unresectable pancreatic cancer on the basis of previous randomized trials (1–3). However, prognosis remains poor, with a reported median survival time of only approximately 10 months. Distant metastases were the main cause of treatment failure after chemoradiotherapy with 5-FU (4). Although the potent radiosensitizing property of 5-FU is the rationale for chemoradiotherapy using 5-FU, this therapy is unlikely to be effective against systemic metastases of pancreatic cancer. A more effective systemic treatment might be essential to control distant metastases and subsequently prolong patient survival.

S-1 is a novel oral fluoropyrimidine preparation that was designed to improve the antitumor activity of 5-FU while reducing gastrointestinal toxicity. In S-1, tegafur is combined with 5-chloro-2, 4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a 1:0.4:1 molar concentration ratio (5). Generally, when administered intravenously, more than 85% of 5-FU is rapidly catabolized by dihydropyrimidine dehydrogenase (DPD) (6). Gimeracil is a competitive inhibitor of DPD and 180 times more potent than uracil, which is the DPD inhibitor included in UFT; thus, an effective concentration of 5-FU is maintained both in plasma and tumor tissues (7). Oteracil inhibits the phosphorylation of 5-FU in the gut and thereby reduces the gastrointestinal toxicity of 5-FU (8).

Recently, S-1 has shown favorable antitumor activity in several Phase II studies for various solid tumors including

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pancreatic cancer. In a recent Phase II study of S-1 for metastatic pancreatic cancer, S-1 demonstrated promising antitumor activity with a response rate of 37.5% and median survival time of 9.2 months (9). Furthermore combination chemotherapy with S-1 and gemcitabine has shown excellent efficacy with a response rate of 44%–48% and a median survival of 10.1–12.5 months in patients with metastatic pancreatic cancer (10, 11). S-1 is regarded as a promising agent for the management of unresectable advanced pancreatic cancer (12), and a randomized Phase III study is ongoing to evaluate the efficacy of S-1 versus gemcitabine vs. S-1 plus gemcitabine.

Although no randomized trials have been performed, the antitumor activity of S-1 for metastatic pancreatic cancer seems to be better than that of 5-FU infusion, which has been used to treat locally advanced pancreatic cancer. Oral S-1 also has a great clinical advantage because the risks of complications associated with intravenous administration are avoided. Moreover, a recent preclinical study has shown that gimeracil, the DPD inhibitor included in S-1, is a potent radiosensitizer (13). Preclinical studies showed that S-1 and fractionated radiotherapy was more effective than either agent alone (14).

We considered oral S-1 to be an attractive alternative to 5-FU infusion in the treatment of locally advanced pancreatic cancer and performed a Phase I study (15). In that study, we suggested that the daily dose of S-1 recommended for systemic chemotherapy could be combined with the conventional dose radiotherapy with acceptable toxicity. This combination therapy was well tolerated and showed outstanding antitumor effect. Thus, we planned a Phase II study to further evaluate the safety and efficacy of S-1 combined with radiotherapy in patients with unresectable locally advanced pancreatic cancer.

METHODS AND MATERIALS

Eligibility

Patients with histopathologically proven, unresectable, locally advanced adenocarcinoma of the pancreas were eligible for this study. Computed tomography (CT) criteria for unresectability was defined as invasion of the superior mesenteric artery or celiac axis or the bilateral stenosis of the portal vein. Patients with distant metastases were excluded. Eligible patients were at least 20 years old with an Eastern Cooperative Oncology Group performance status of $\leq$2 and had adequate organ function (leukocytes $\geq$4000/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.5 g/dL, normal serum creatinine and blood urea nitrogen, a serum glutamic oxaloacetic transaminase (GOT) $\leq$2.5 times the upper normal limit (UNL), a serum glutamic pyruvic transaminase (GPT) $\leq$ 2.5 times the UNL and serum bilirubin $\leq$ 2.0 mg/dL.) Patients with jaundice caused by biliary obstruction were required to have a total bilirubin concentration of 3.0 mg/dL or less after biliary drainage.

Patients were excluded if they had received systemic therapy or radiotherapy, had a concomitant malignancy, active inflammatory bowel disease, active gastric/duodenal ulcer, active infection, severe heart disease, mental disorder, or other severe concurrent disease. Pregnant or lactating women were also excluded.

This prospective Phase II study was performed according to the guidelines of the Declaration of Helsinki as amended in Edinburgh, Scotland, in October 2000, and the protocol was approved by the Institutional Review Board of Chiba Cancer Center and Chiba University Graduate School of Medicine. All patients gave their written informed consent before entry into this study.

Treatment

Radiotherapy was initiated on Day 1 of the study using 10-MV photons. A fractional daily dose of 1.8 Gy (5 days/week) at the isocenter, up to a total dose of 50.4 Gy, was prescribed. Treatment planning was performed using a CT simulator for all patients. CT images were acquired using a 3-mm-slice thickness with free breathing. The dose distribution and dose–0volume histogram were calculated with a three-dimensional (3D) treatment planning system. The gross tumor volume was taken to be the primary tumor and metastatic lymph nodes identifiable on CT scan. The clinical target volume was defined as the gross tumor volume plus a 0.5-cm margin and the planning target volume was defined as the clinical target volume plus 1–1.5 cm for daily patient setup variation. No prophylactic nodal irradiation was performed. The clinical target volume was encompassed within the 95% isodose line. To avoid renal toxicity, we allowed a maximum of 50% of both kidneys to be exposed to 20 Gy. The dose to the liver was limited to 50% of the volume receiving <30 Gy. Radiation to the spinal cord was limited to 40 Gy.

S-1 (Taiho Pharmaceutical, Tokyo, Japan) was administered orally twice a day at a dose of 80mg/m^2/day from Day 1–14 and 22–35 in concurrent with radiotherapy. Three initial doses were established according to the body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA < 1.50 m^2, 100 mg/day; and 1.50 m^2 $\leq$ BSA, 120 mg/day. Two weeks after the completion of chemoradiotherapy, maintenance chemotherapy with S-1 was administered for 28 days every 6 weeks until progression.

Dose modification

S-1 was temporally discontinued until recovery when any of the following conditions were encountered: leukocytes <2,000/mm^3, neutrophils <1,000/mm^3, hemoglobin <8.0 g/dL, platelets <75,000/mm^3, serum GOT/GPT $\geq$150 IU/L, serum total bilirubin $\geq$3.0 mg/dL, serum creatinine $\geq$1.5 mg/dL, or when Grade 3 nonhematologic toxicity was observed. The dose of S-1 was reduced by 20 mg/day if Grade 4 hematologic toxicity or Grade 3 nonhematologic toxicity occurred. Radiation therapy was withheld when Grade 4 hematologic or Grade 3 nonhematologic toxicity occurred, until resolution of the toxicities.

Pretreatment and follow-up evaluation

The pretreatment evaluation included a medical history and physical examination, complete blood cell counts, routine chemistry tests, electrocardiogram, chest X-ray, ultrasonography, and CT of the abdomen and chest with intravenous contrast.

Physical examination, complete blood cell counts and serum biochemistry tests were performed at least weekly during chemoradiotherapy. Upper gastrointestinal endoscopy was performed before study entry and within 2 weeks after completing treatment to evaluate acute gastrointestinal toxicities. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Follow-up CT was performed at the completion of radiotherapy, and then repeated every 2 months. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors by three independent radiologists. The best overall response was recorded for each patient. The overall response rate was defined as the percentage of patients achieving either complete response (CR) or partial response (PR). Disease control rate was defined as

the proportion of patients who achieved CR, PR, or stable disease (SD) as the best overall response. Serum CA 19-9 levels were evaluated monthly using a commercially available chemiluminescent enzyme immunoassay kit based on the two-step sandwich method (CL-EIA). A value of 39.5 U/mL was defined as the upper normal limit. Progression-free survival and overall survival were calculated from the first day of treatment.

Statistical analysis

The primary objective of this study was to evaluate the response rate of S-1 concurrent with radiotherapy in patients with locally advanced pancreatic cancer. The secondary objectives were to evaluate toxicity, progression-free survival, and overall survival.

The number of patients required for the study was calculated according to the optimal two-stage design. The threshold response rate and expected response rate were 10% and 30%, respectively. The sample size was 29 patients with a type I error of 5% and a test power of 80%.

An intent-to-treat analysis was performed for all included patients. Time-related parameters were analyzed using Kaplan–Meier method.

RESULTS

Patient characteristics

Thirty-four patients from two institutions were enrolled in this study between September 2004 and July 2008 (Fig. 1). The characteristics of the eligible patients are summarized in Table 1. Eighteen of the patients were men and 16 were women, with a median age of 63 years. Most patients (82%) had an Eastern Cooperative Oncology Group performance status of 0 or 1. The most common tumor site was the pancreatic head (59%), with a median tumor size of 3.9 cm.

Twenty-nine patients (85%) completed the planned chemoradiotherapy without a dose reduction of S-1 or radiation. Four patients required a dose reduction of S-1 because of adverse events: Grade 4 neutropenia in one patient, nausea, and anorexia in one patient, skin rash in one, and urinary tract infection in one patient. The remaining patient discontinued the protocol treatment because of withdrawal of consent.

Thirty-three patients (97%) received maintenance chemotherapy with S-1 after chemoradiotherapy, for a total of 173 cycles (median, 4; range, 0–16). When tumor progressed, most patients (28/31, 90%) received a second-line treatment with gemcitabine.

Toxicity

All treated patients (n = 34) were assessed for toxicities. Toxicity during chemoradiotherapy is listed in Table 2. Hematologic toxicity was relatively mild, and the most common Grade 3 toxicity was anorexia (24%). Other Grade 3 or 4 nonhematologic toxicities included nausea (12%), skin rash (3%), and urinary tract infection (3%). There was no life-threatening toxicity, and no treatment-related deaths occurred. We performed upper gastrointestinal endoscopy after the combination therapy in 29 patients: 6 had gastric or duodenal ulcers and 17 had gastritis or duodenitis. Most of these patients had few symptoms except for anorexia and recovered with medical treatment. No Grade 3 or 4 gastrointestinal ulcers were observed.

Grade 3 or 4 toxicity during maintenance chemotherapy is summarized in Table 3. The most common Grade 3 or 4 toxicity was anemia. Grade 3 nonhematologic toxicities were observed in five patients: hemorrhagic gastritis in three, acute cholecystitis in one, and liver abscess in one. Although one of the three patients who experienced hemorrhagic gastritis recovered with conservative treatment, the remaining two patients required endoscopic hemostasis. The patient who experienced acute cholecystitis 12 months after radiotherapy required surgical treatment and 2 months' hospitalization. The patient who developed a liver abscess 12 months after chemoradiotherapy recovered with conservative treatment.

Response and survival

All treated patients (n = 34) were evaluable for tumor response. At the initial evaluation immediately after chemoradiotherapy, partial response was seen in four patients (12%). Stable disease was seen in 29 patients, and progressive disease in only one patient (3%). Subsequently, 10 additional patients with stable disease at the initial evaluation achieved partial response during maintenance chemotherapy. Thus, 14 (41%) of the 34 patients (95% confidence interval [CI], 25%–58%) showed partial response during the follow-up period. Disease control rate (partial response plus stable disease) was 97% (33/34).

Twenty-nine patients had elevated CA 19-9 levels (median, 1008; range, 83–7184 U/mL) without jaundice before treatment. The minimal CA 19-9 level after treatment (median, 52; / range, 3–4,140 U/mL) decreased more than 50% in 27 (93%) of these 29 patients and showed a normal value in 13 (45%).

At the time of analysis, disease progression was noted in 31 patients. The pattern of initial disease progression was distant metastases in 13 patients (38%), local progression of the pancreatic tumor in 9 (26%), both in 6 (18%), and deterioration of general condition in 3 patients (9%; Table 4). Among the patients, regional lymph nodes recurrence was seen in two patients. Both patients had concurrent distant metastases. The median progression-free survival was 8.7 months (95% CI, 7.0–10.4 months). The median survival time and 1-year survival rate were 16.8 months (95% CI, 12.9–20.7 months) and 70.6% (95% CI, 55.3%–85.9%), respectively (Fig. 2).

DISCUSSION

Chemoradiotherapy using 5-FU has been the mainstay treatment for unresectable, locally advanced pancreatic cancer. We used S-1 instead of 5-FU infusion, in combination with radiotherapy, because of its favorable antitumor activity against metastatic pancreatic cancer and convenient oral administration. In our protocol, the standard daily dose of S-1 for systemic chemotherapy was combined with concurrent radiotherapy based on our Phase I study (15). Maintenance chemotherapy with S-1 was administered to delay or reduce the development of distant metastases in responding or stable patients after S-1 and radiotherapy. In addition, second-line chemotherapy with gemcitabine was delivered in most cases after treatment failure. The rationale of our protocol was to

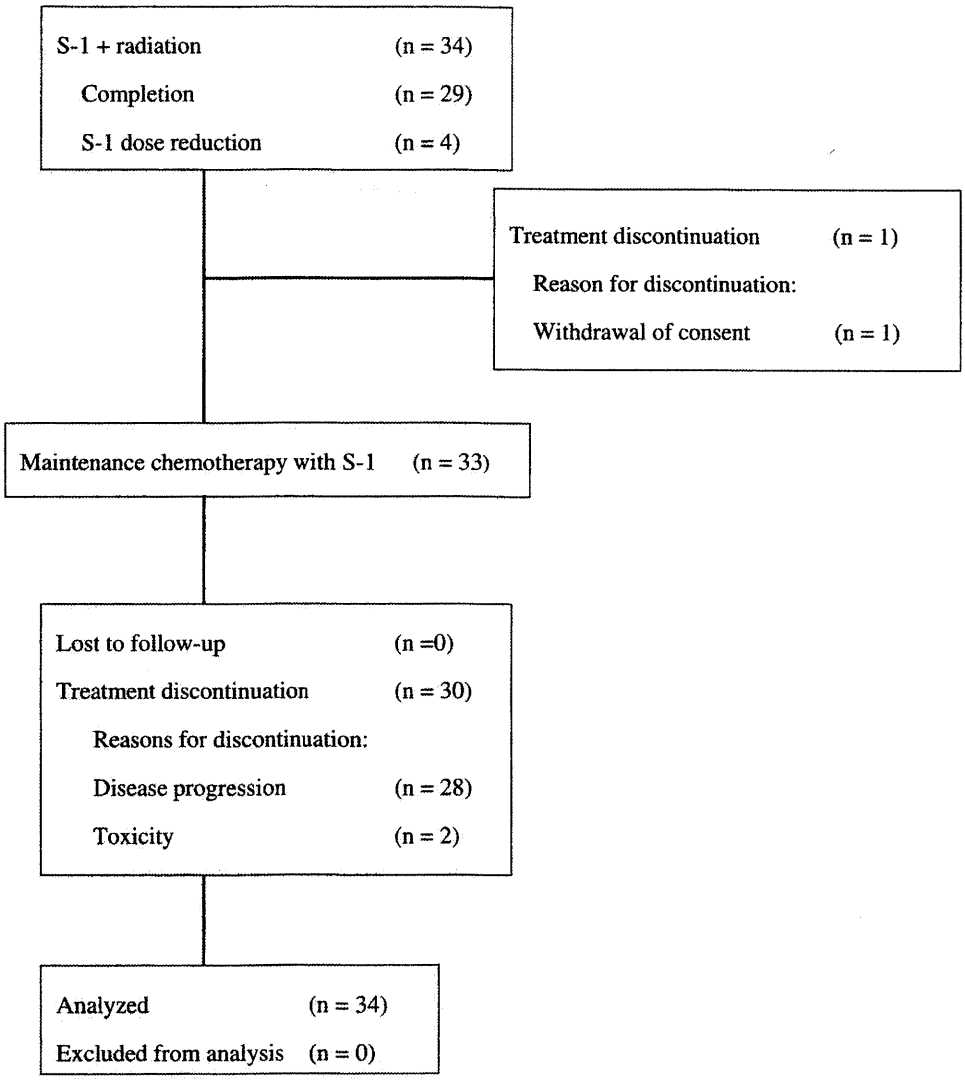

Fig. 1. Study schema.

intensify systemic activity while maintaining the patient's quality of life by using an oral anticancer agent.

To date, there is little information on the safety and efficacy of this combination therapy not only in patients with pancreatic cancer, but in those with other types of tumors as well. In this study, S-1 at the dose recommended for systemic chemotherapy and the standard dose of radiotherapy were well tolerated and feasible in patients with locally advanced pancreatic cancer. The most common toxicity during chemoradiotherapy was anorexia, with Grade 3 toxicity occurring in 24% of the patients. Hematologic toxicity was relatively mild. No life-threatening toxicity was experienced. We performed upper gastrointestinal endoscopy after chemoradiotherapy to assess acute gastrointestinal toxicity but did not detect Grade 3 or 4 ulcers. As for radiation late toxicity, hemorrhagic gastritis was considered to require special attention. Acute cholecystitis and liver abcess were considered to be caused mainly by biliary stent occlusion.

Table 1. Patient characteristics

No. of patients	34
Sex	
Men	18
Women	16
Age, years	
Median (range)	63 (42–78)
ECOG performance status	
0	9
1	19
2	6
Site of tumor	
Head	20
Body-tail	14
Largest dimension, cm	
Median (range)	3.9 (2.9–6.6)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

In this study, S-1 combined with radiotherapy showed promising antitumor effect in patients with locally advanced pancreatic cancer. Although it is difficult to compare our results with those of other studies, the response rate of 41%, the disease control rate of 97%, the CA 19-9 response rate of 93% and the median survival time of 16.8 months compare well with the outcomes of other chemoradiotherapy regimens (Table 5) (4, 16–20). One possible explanation for these

Table 2. Toxicity during chemoradiation (n = 34)

Toxicity	Grade 1 or 2	Grade 3	Grade 4
Hematological toxicity			
Leukocytopenia	26	3	0
Neutropenia	15	2	1
Anemia	15	0	0
Thrombocytopenia	21	1	0
Nonhematological toxicity			
Anorexia	19	8	0
Nausea	18	4	0
Vomiting	7	0	0
Diarrhea	5	0	0
Elevation of GOT/GPT	11	0	0
Elevation of creatinine	1	0	0
Skin rash	7	1	0
Urinary tract infection	0	1	0
Gastric/duodenal ulcer*	6	0	0
Gastritis/duodenitis*	17	0	0
GI hemorrhage	0	0	0

Abbreviations: GI = gastrointestinal; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

* Twenty-nine patients received GI endoscopy after chemoradiotherapy.

promising results, we suppose, may be the use of an agent that has demonstrated high response rate for metastatic pancreatic cancer from the beginning of radiotherapy. Indeed, only one patient developed distant metastases at the initial evaluation after chemoradiotherapy. In addition, it also seemed important that the compliance of our regimen was relatively good because of the acceptable toxicity profile and convenient oral administration of S-1. As a result, most patients received the planned chemoradiotherapy and following maintenance chemotherapy. Moreover, 90% of the patients received second-line chemotherapy with gemcitabine after treatment failure.

In this study, to reduce toxicity and improve therapeutic compliance, radiotherapy was performed using 3D treatment planning without conducting prophylactic nodal irradiation. The clinical target volume (CTV) of conventional chemoradiotherapy for pancreatic cancer usually includes the regional lymph nodes irrespective of the presence or absence of nodal metastases, which may result in severe gastrointestinal toxicity and limit the delivery of the prescribed dose of radiotherapy or following maintenance chemotherapy. In an attempt to reduce toxicity and combine radiotherapy with full-dose gemcitabine, McGinn *et al.* (21) investigated the usefulness of 3D conformal radiotherapy not including prophylactic nodal irradiation. Our group has also reported the feasibility of involved-field irradiation with a 15-20 mm margin where only the primary tumor and clinically enlarged lymph nodes were included in the CTV without using prophylactic nodal irradiation (22). The rationale for reducing the irradiation field size is to reduce radiation toxicity and subsequently to deliver sufficient systemic chemotherapy. In this study, as described earlier, severe acute gastrointestinal mucositis was rare and treatment compliance was satisfactory. Locoregional lymph nodes recurrence was seen in only two patients, and we therefore suggest that the reduction of the radiation field size did not result in excess locoregional failure.

To date, in an attempt to prolong the survival of patients with locally advanced pancreatic cancer, many studies using novel agents such as gemcitabine (16, 17), capecitabine (18), paclitaxel (19), oxaliplatin (20), or bevacizumab (23), as well

Table 3. Grade 3–4 toxicity during maintenance chemotherapy (n = 33)

Toxicity	Grade 3	Grade 4
Leukocytopenia	2	0
Neutropenia	3	0
Anemia	2	2
Thrombocytopenia	0	0
Anorexia	1	0
Nausea/vomiting	0	0
Diarrhea	0	0
Elevation of GOT/GPT	0	0
Skin rash	0	0
Hemorrhagic gastritis	3	0
Acute cholecystitis	0	1
Liver abscess	1	0

Abbreviations: GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

Table 4. Patterns of initial disease progression (n = 34)

	No. of patients (%)
None	3 (9%)
Distant metastases	13 (38%)
Liver	3
Peritoneum	4
Liver and peritoneum	1
Lung	2
Pleura	2
Bone	1
Local progression of the pancreatic tumor	9 (26%)
Local progression of the pancreatic tumor and distant metastases	6 (18%)
Liver	1
Peritoneum	4
Lung	1
Deterioration of general condition	3 (9%)

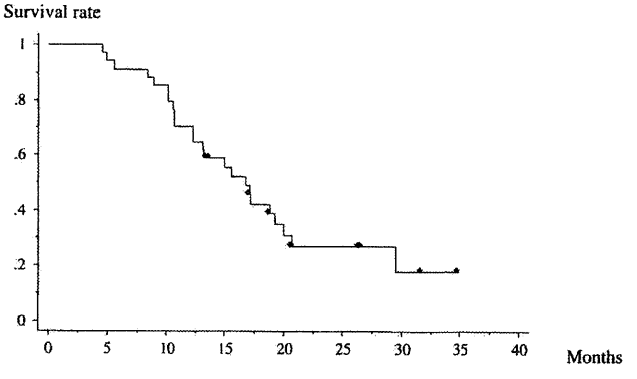

Fig. 2. Kaplan–Meier overall survival.