

Adjuvant Chemotherapy With Gemcitabine vs Observation in Patients Undergoing Curative-Intent Resection of Pancreatic Cancer

A Randomized Controlled Trial

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WITH AN ESTIMATED NUMBER of 232 000 new cases per year, pancreatic cancer is among the most common malignancies worldwide.¹ Moreover, it is one of the most lethal cancers, as indicated by a mortality incidence ratio of 98%.¹ Pancreatic cancer is the fourth leading cause of death from cancer in the United States, with 32 300 deaths estimated in 2006.² Sur-

Context The role of adjuvant therapy in resectable pancreatic cancer is still uncertain, and no recommended standard exists.

Objective To test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more.

Design, Setting, and Patients Open, multicenter, randomized controlled phase 3 trial with stratification for resection, tumor, and node status. Conducted from July 1998 to December 2004 in the outpatient setting at 88 academic and community-based oncology centers in Germany and Austria. A total of 368 patients with gross complete (R0 or R1) resection of pancreatic cancer and no prior radiation or chemotherapy were enrolled into 2 groups.

Intervention Patients received adjuvant chemotherapy with 6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks (n=179), or observation ([control] n=175).

Main Outcome Measures Primary end point was disease-free survival, and secondary end points were overall survival, toxicity, and quality of life. Survival analysis was based on all eligible patients (intention-to-treat).

Results More than 80% of patients had R0 resection. The median number of chemotherapy cycles in the gemcitabine group was 6 (range, 0-6). Grade 3 or 4 toxicities rarely occurred with no difference in quality of life (by Spitzer index) between groups. During median follow-up of 53 months, 133 patients (74%) in the gemcitabine group and 161 patients (92%) in the control group developed recurrent disease. Median disease-free survival was 13.4 months in the gemcitabine group (95% confidence interval, 11.4-15.3) and 6.9 months in the control group (95% confidence interval, 6.1-7.8; $P<.001$, log-rank). Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group (median, 22.1 months; 95% confidence interval, 18.4-25.8; estimated survival, 34% at 3 years and 22.5% at 5 years) and the control group (median, 20.2 months; 95% confidence interval, 17-23.4; estimated survival, 20.5% at 3 years and 11.5% at 5 years; $P=.06$, log-rank).

Conclusions Postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation alone. These results support the use of gemcitabine as adjuvant chemotherapy in resectable carcinoma of the pancreas.

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See also p 311 and Patient Page.

gery is the only curative treatment option for this cancer entity. However, due to the aggressive biology of the tumor and the lack of early disease-specific signs and symptoms, only a small minority of patients present with potentially resectable disease at the time of diagnosis. Even with surgery, prognosis remains poor due to the high propensity of the tumor for locoregional, including hepatic, recurrence.^{3,4} In the National Cancer Database population, 5-year overall survival in patients undergoing pancreatectomy was only 23.4%.⁵ Therefore, surgery alone is clearly an inadequate approach to achieve long-term disease control in patients with resectable pancreatic cancer.

There is conclusive evidence in patients with early breast cancer that postoperative adjuvant chemotherapy, hormonal therapy, or postoperative adjuvant chemotherapy and hormonal therapy combined reduce the rate of recurrence and improve long-term survival after primary surgery.⁶⁻⁸ Adjuvant chemotherapy has also become standard practice in stage III colorectal cancer.⁹ For stage II colon cancer and gastric cancer, evidence is less clear and the clinical role of adjuvant treatment still remains a topic of debate.^{10,11} Since the 1980s, several studies of adjuvant therapy have also been conducted in patients with resected pancreatic cancer, but the few randomized controlled studies have provided inconsistent results.¹²⁻¹⁷ Various chemoradiation and chemotherapy regimens were used in these studies, all of which included fluorouracil. This antimetabolite has long been the only available drug that offered some promise in the palliative treatment of advanced pancreatic cancer, but objective responses were rarely achieved. The moderate activity of fluorouracil may therefore explain the unsatisfactory results reported for fluorouracil-containing adjuvant regimens in patients undergoing pancreatectomy.

The development of gemcitabine may be considered a major advance in

the treatment of pancreatic cancer. Gemcitabine is a difluorinated analog of the naturally occurring nucleoside deoxycytidine, and has shown significant clinical activity in a variety of solid tumors including pancreatic cancer. Moreover, gemcitabine has a good safety profile with a low incidence of grade 3 or 4 toxicities.¹⁸ In 1997, Burris et al reported the results of their landmark phase 3 study that demonstrated significant improvements both in survival and clinical benefit (pain relief, improved performance status, or both) with single-agent gemcitabine compared with fluorouracil as first-line chemotherapy for advanced pancreatic cancer.¹⁹ In the same year, we initiated our phase 3 study CONKO-001 (Charité Onkologie) to compare adjuvant gemcitabine with no postoperative anticancer therapy in patients undergoing complete, curative-intent resection of pancreatic cancer. We hypothesized that tumor control in these patients could be improved by postoperative gemcitabine treatment, resulting in longer disease-free survival.

METHODS

Study Design

CONKO-001 was an open, multicenter, randomized controlled trial with an active treatment group (adjuvant gemcitabine) and a control group (observation only). The trial was initiated by the German Study Group for Pancreatic Cancer, which is affiliated with the German Cancer Society (Deutsche Krebsgesellschaft, DKG). The coordinating center of the trial was at Charité School of Medicine, Berlin, Germany. Since adjuvant chemotherapy with gemcitabine is usually given on an outpatient basis, the participating centers included oncology departments and oncology clinics within hospitals as well as community oncology practices in Germany and Austria. The study was conducted in accordance with the principles of good clinical practice, the ethical principles stated in the current revision of the Declaration of Helsinki,

and local legal and regulatory requirements. The protocol was approved by the institutional review board at each study site and all patients provided written informed consent.

Patient Selection

Patients with histologically verified pancreatic cancer who had macroscopic complete resection and no prior radiation or neoadjuvant chemotherapy were eligible for the study. The patients were required to have stage T1-4 N0-1 M0 disease prior to surgery. Other eligibility criteria included being aged 18 years or older, having a Karnofsky performance status of 50% or greater, adequate bone marrow function (leukocytes $\geq 3.5 \times 10^9/L$ [3500/ μ L], platelets $\geq 100 \times 10^9/L$, hemoglobin ≥ 80 g/L [8 g/dL]), patient availability, and adherence to long-term follow-up for at least 2 years after surgery.

Patients were excluded if they had active infection, impaired coagulation (international normalized ratio and/or activated partial thromboplastin time > 1.5 times the upper limit of normal), transaminases greater than 3 times the upper limit of normal, serum creatinine greater than 1.5 times the upper limit of normal, postoperative tumor markers (carcinoembryonic antigen/cancer antigen [CEA/CA19-9]) greater than 2.5 times the upper limit of normal, or a history of another malignant disease other than carcinoma in situ of the uterine cervix or adequately treated basal cell carcinoma of the skin. Pregnant or breastfeeding women were also excluded from the study. Non-pregnant women of childbearing age were required to be using reliable contraceptive methods for the duration of the study until at least 3 months after its termination.

Procedures and Treatment

Standard surgical procedures were used depending on the extent of tumor involvement and according to institutional guidelines. Histologic examinations of the surgical specimens were performed in the pathology depart-

ments of the recruiting centers. The original protocol required patients to have R0 resection, defined as histologically tumor-free surgical margins. However, because the study protocol did not require a standardized system of pathologic assessment or pathology quality control, it was decided to amend the protocol to also include patients with R1 resection; this offered the possibility of performing separate end point analyses in patients with R0 and R1 resection to compare the effect of adjuvant gemcitabine in these subgroups. The amendment was implemented on November 17, 1998, 4 months after opening the study and after recruitment of 9 patients.

Eligible patients were randomly assigned on a 1:1 basis to either of 2 study groups, using a central randomization procedure with stratification for resection status (R0 vs R1), T status (T1-2 vs T3-4), and nodal status (N⁻ vs N⁺) according to the standards of TNM classification. Randomization using sealed envelopes was conducted in the first 73 patients by a statistician at the German Cancer Research Center (Deutsches Krebsforschungszentrum, Heidelberg, Germany), while randomization for the remaining patients was performed at the coordinating center of the trial using a computer-generated procedure. Patients in the gemcitabine group received adjuvant chemotherapy with 6 cycles of gemcitabine every 4 weeks. Each chemotherapy cycle consisted of 3 weekly infusions of gemcitabine 1000 mg/m² given by intravenous infusion during a 30-minute period, followed by a 1-week pause. It was recommended to start adjuvant chemotherapy between day 10 and day 42 following surgery or after wound healing. Patients in the control group received no postoperative chemotherapy (observation only). Patients were withdrawn from the study for any of the following reasons: recurrent disease, patient's wish, unacceptable toxicity of treatment, pregnancy or inadequate contraception in a woman of childbearing potential, or if a

patient was likely to benefit more from an alternative treatment according to the investigator's discretion.

Dose Modification

Patients in the gemcitabine group received all cycles of gemcitabine at full dose unless modification of the dose was required based on weekly assessments of hematology on days 1, 8, and 15 prior to each dosing, and grading of nonhematologic toxicities prior to each new chemotherapy cycle. A leukocyte count greater than $3.5 \times 10^9/L$ (3500/ μL) and a platelet count greater than $100 \times 10^9/L$ were required for each full dose of gemcitabine to be administered. For leukocyte counts between 2.0 and $3.49 \times 10^9/L$ (2000-3490/ μL) and platelets between 75 and $100 \times 10^9/L$, the subsequent dose or doses of gemcitabine within the same cycle were reduced to 75% of the starting dose. Leukocyte counts of less than $2.0 \times 10^9/L$ (2000/ μL), platelet counts of 50 to $74 \times 10^9/L$, or any grade 3 nonhematologic toxicity other than alopecia or nausea/vomiting, required a dose reduction to 50% of the starting dose or discontinuation of chemotherapy, depending on the investigator's decision. Chemotherapy had to be discontinued if platelet counts declined to less than $50 \times 10^9/L$ or whenever a grade 4 nonhematologic toxicity occurred. The dose could again be increased up to the starting dose in the next cycles provided that the reduced dose was well tolerated. In the event of febrile neutropenia, thrombocytopenia grade 3 or 4, or bleeding, however, treatment had to be discontinued until resolution of cytopenia and continued in the next cycle at 75% of the starting dose of the prior cycle. Again, there was an option for re-increasing the dose in the following cycles. Omitted doses of gemcitabine were not replaced. If a day-1 dose was discontinued or omitted, the next delivered dose was counted as day 1 of this cycle. If a day-8 dose was discontinued or omitted, this was considered a treatment pause and the next delivered dose counted as the day-1 dose of a new cycle.

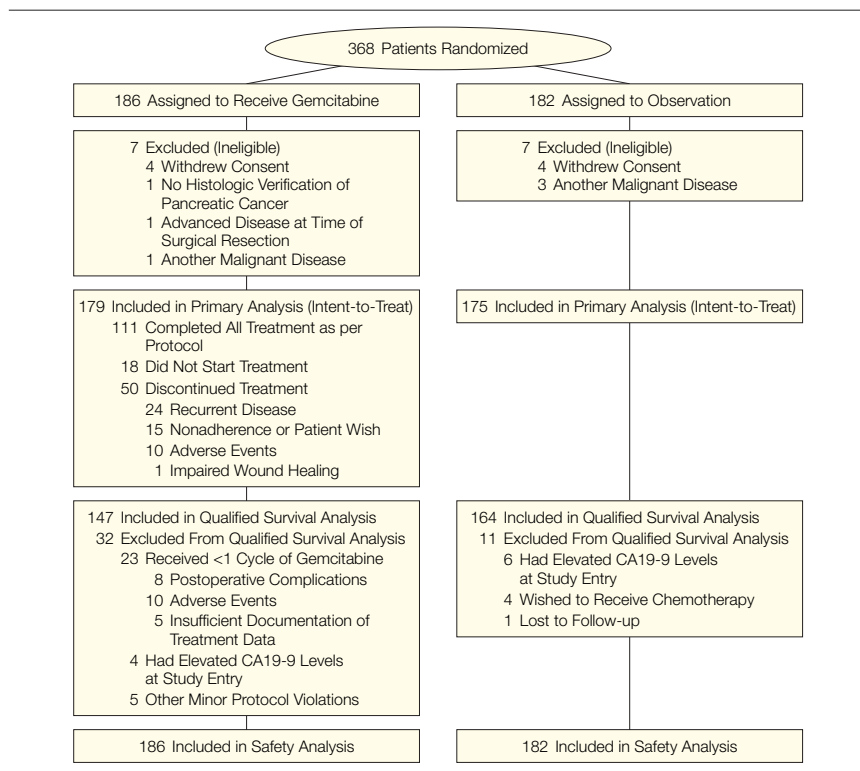
During the study, no other antineoplastic therapies including chemotherapy, immunotherapy, radiotherapy, or experimental agents were allowed. Patients who required specific antitumor therapy to treat recurrent disease were withdrawn from the study.

Assessments

Prior to enrollment in the study, all patients underwent a complete medical history and physical examination including routine laboratory studies (hematology, chemistry, urinalysis), tumor markers CEA and CA19-9, vital signs, and body weight and height. Performance status was assessed using the Karnofsky scale, and quality of life using the Spitzer Quality-of-Life Index.²⁰ A self-assessment questionnaire of pain intensity and mood based on a visual analog scale from 0 to 10 was also applied. Tumor assessments included abdominal computed tomography, magnetic resonance imaging, and ultrasound. Chest radiography done as part of preoperative work-up was sufficient. During the study, vital signs and complete blood counts were obtained weekly on days 1, 8, and 15 prior to each administration of gemcitabine in the gemcitabine group, and every 4 weeks in the control group. Additional 4-weekly assessments in both study groups included serum biochemistry, tumor markers, performance status, quality of life, and toxicities/adverse events. Abdominal ultrasound to detect recurrent disease was performed every 8 weeks. After completion of adjuvant chemotherapy in the gemcitabine group, and after 6 months in the control group, computed tomography imaging was repeated. Patients' cases were then followed every 8 weeks until death to assess adverse events, performance status, quality of life, disease status, and survival. Toxicities were graded according to the World Health Organization classification.

Quality Assurance

All efforts were made to ensure the proper conduct of the trial as well as

Figure 1. Flow of Study Participants.

the accuracy, completeness, and reliability of the acquired data as specified in the protocol. All essential aspects of the protocol, including the completion of the case report forms, were discussed in detail with the site investigators at an educational meeting that took place immediately before the start of the trial. If necessary, the participating centers were provided with written instructions. The trial was monitored by a specialized oncology contract research organization (SKM, now i3 Research SKM Oncology, Wiesbaden, Germany).

End Points and Statistical Methods

The primary end point of the trial was disease-free survival, which was defined as the time from randomization to the date of local or distant recurrence or death. The date of recurrence was defined as the date of the first subjective symptom heralding relapse, or the date of documentation by diagnostic imaging techniques of recurrent disease, independent of site, whichever oc-

curred first. The study was designed to reject the null hypothesis that adjuvant chemotherapy with gemcitabine did not improve disease-free survival. Secondary end points included toxicity, quality of life (Spitzer index), and overall survival, defined as the time from randomization to death from any cause.

Calculation of the sample size was based on the assumption that median disease-free survival of completely resected patients with pancreatic cancer would be 18 months in the gemcitabine group and less than 12 months^{17,21} in the control group. To detect a difference in disease-free survival of 6 months with a statistical power of 90% at a 2-sided .05 significance level, and assuming: (1) a 20% dropout rate due to ineligibility; (2) a 3-year recruitment period; and (3) a follow-up of at least 2 years, a sample size of 184 patients was required for each group. The study protocol required continuous monitoring for deaths, toxicities, and serious adverse events. Premature ter-

mination of the study had to be considered at any time if unacceptable toxicity was reported for more than 10% of the patients in the adjuvant treatment arm. A formal interim analysis was done after enrollment of the first 40 patients using O'Brien-Fleming adjustment for α error control.

Data analysis was undertaken using the Statistical Package for the Social Sciences, German version 6.1 (SPSS Inc, Chicago, Ill). Kaplan-Meier curves of estimated disease-free survival and overall survival were generated, and comparisons between the groups were performed using a 2-sided log-rank test. Median disease-free survival and overall survival times with 95% confidence intervals (CIs) were also determined. Results were considered significant at $P \leq .05$. As defined in the protocol, the survival analyses were based on the intent-to-treat population, which included all eligible patients enrolled in the study. The protocol also required "qualified" survival analyses based on the population of patients who had received at least 1 complete cycle of gemcitabine in the adjuvant treatment group and no adjuvant cytotoxic or radiation therapy in the control group, respectively; patients with even minor violations of entry criteria were excluded from this analysis. Both intent-to-treat and qualified survival analyses were also performed in subpopulations stratified by resection status (R0 vs R1), T status (T1-2 vs T3-4) and nodal status (N⁻ vs N⁺). Longitudinal comparisons between the study groups were made for body weight, Karnofsky index, quality of life, and tumor markers CEA and CA19-9, based on all patients with available data. All patients with documented toxicity data were included in the safety analysis.

RESULTS

Patients

Between July 1998 and December 2004, a total of 368 patients were recruited into the study from 88 centers in Germany and Austria. The patients were randomized to the gemcitabine group (n = 186) and the observation group (control) (n = 182). All

randomized patients were included in the safety analysis. One hundred seventy-nine patients in the gemcitabine group and 175 patients in the control group met the eligibility criteria and constituted the intent-to-treat population for the primary end point analysis (FIGURE 1). The baseline characteristics of the eligible patients are shown in TABLE 1. There were only minor differences in the demographic and tumor characteristics between the study groups. All but 11 patients had adenocarcinoma. The majority had T3 N1 disease prior to surgery and underwent R0 resection. The median time from surgery to the start of chemotherapy in the gemcitabine group was 36 days (interquartile range, 28-43 days).

Treatment Delivery

The median number of cycles administered to the 179 patients randomized to the gemcitabine group was 6, and 111 patients (62%) were given the full number of 6 cycles as specified in the protocol. Ninety percent of the patients received at least 1 dose, and 87% received at least 1 full cycle of adjuvant chemotherapy with gemcitabine. The average weekly dose of gemcitabine was 700 mg/m², and the median relative-dose intensity was 86%. The main reason for not starting protocol treatment in 18 patients was impaired wound healing and other postoperative complications or concomitant diseases. The reasons for discontinuation of adjuvant chemotherapy in 50 patients included recurrent disease (24 patients, 48%), patient wish or nonadherence (15 patients, 30%), adverse events (10 patients, 20%), and impaired wound healing (1 patient, 2%). Dose modifications occurred mainly as a result of leukopenia, nausea, infection, thrombocytopenia, and pain.

Toxicity

There were 186 patients in the gemcitabine group and 182 in the control group evaluated for toxicity. Adjuvant chemotherapy with gemcitabine was well tolerated, and grade 3 or 4 toxicities occurred infrequently (TABLE 2).

Moreover, no increase in hematologic or nonhematologic toxicity was seen over the course of the 6 cycles of gemcitabine treatment. A total of 62 serious adverse events were reported in 41 patients (26 patients in the gemcitabine group and 15 patients in the control group) during the study. In 5 out of 26 patients experiencing a serious adverse event in the gemcitabine group, this was considered treatment-related. Neither of the 2 fatal events occurring in the study (1 anastomotic ulceration, 1 hemorrhagic shock, both occurring in the gemcitabine group) were considered gemcitabine-related.

Efficacy

With a median follow-up of 53 months (range, 9-96), recurrent disease developed in 133 of 179 eligible patients

(74.3%) in the gemcitabine group and 161 of 175 patients (92.0%) in the control group. The pattern of recurrence was comparable in both groups. Local recurrence with or without distant metastasis occurred in 34% of relapsed patients in the gemcitabine group and 41% of those in the control group. Distant metastasis was the only manifestation of recurrent disease in 56% of relapsed patients in the gemcitabine group and 49% in the control group. The primary site of distant relapse was the liver (36% in the gemcitabine group and 37% in the control group). The site of recurrence was not reported in 10% of the patients in either group because the diagnosis was made solely on a clinical basis in these cases.

The estimated median disease-free survival was 13.4 months (95% CI,

Table 1. Baseline Characteristics of Eligible Patients

	No. (%)	
	Gemcitabine Group	Observation Group (Control)
No. of patients	179	175
Age, median (range), y	62 (34-82)	61 (36-81)
Sex		
Women	74 (41)	77 (44)
Men	105 (59)	98 (56)
Days from surgery to randomization		
Median	22	24
Interquartile range	15-32	15-34
Days from resection to start of adjuvant chemotherapy, median (interquartile range)	36 (28-43)	
Karnofsky performance status, median (range)	80 (60-100)	80 (50-100)
Resection status		
R0	145 (81)	148 (85)
R1	34 (19)	27 (15)
Primary tumor size		
T1	7 (4)	7 (4)
T2	18 (10)	17 (10)
T3	146 (82)	146 (83)
T4	8 (4)	5 (3)
Nodal status		
N0	52 (29)	48 (27)
N1	126 (70)	124 (71)
N2	1 (1)	3 (2)
Grading		
1	10 (6)	9 (5)
2	103 (58)	95 (54)
3	63 (35)	68 (39)
Unknown	3 (2)	3 (2)
Histology		
Adenocarcinoma	175 (98)	168 (96)
Other	4 (2)	7 (4)

11.4-15.3) in the gemcitabine group compared with 6.9 months (95% CI, 6.1-7.8) in the control group. The disease-free survival advantage in favor of adjuvant gemcitabine was significant ($P < .001$) (TABLE 3 and FIGURE 2). The estimated disease-free survival rates at 1, 2, 3, and 5 years were 58%, 30.5%, 23.5%, and 16.5% in the gemcitabine group and 31%, 14.5%, 7.5%, and 5.5% in the control group, respectively. The qualified analysis of disease-free survival provided similar results in both groups (median 13.7 months, gemcitabine vs median 6.9 months, control; $P < .001$). Exploratory subgroup analyses in the intent-to-treat population demonstrated that the beneficial effect of adjuvant gemcitabine on disease-free survival was evident for

both patients with R0 and R1 resection (Figure 2), for patients with large and small primary tumors, and those with and without nodal involvement (Table 3). Similar results and significant differences between the 2 groups were obtained for all these subgroups in the qualified patient population.

At the time of analysis, there was a nonsignificant trend for improved overall survival in favor of gemcitabine in the intent-to-treat population ($P = .06$, log-rank; Table 3). Survival estimates were based on 122 events in the gemcitabine group and 137 events in the control group, ie, survival times were censored for 31.8% and 21.7% of the patients in these groups. The survival curves are shown in Figure 2. Median overall survival was 22.1 months in the

gemcitabine group (95% CI, 18.4-25.8) compared with 20.2 months in the control group (95% CI, 17-23.4). The estimated overall survival rates at 1, 2, 3, and 5 years were 72.5%, 47.5%, 34%, and 22.5% in the gemcitabine group and 72.5%, 42%, 20.5%, and 11.5% in the control group, respectively. In the qualified analysis, the overall survival advantage for gemcitabine was significant (median, 24.2 months, 95% CI, 18.4-30.0 vs median, 20.5 months, 95% CI, 17.0-24.0; $P = .02$) for the control group.

In the patient subgroups defined by resection, T and N status, a significant difference in median overall survival in favor of adjuvant gemcitabine was observed for R0 patients (24.4 vs 21.7 months; $P = .047$) and T3-4 patients (22.5 vs 19.9 months; $P = .02$) in the qualified

Table 2. Toxicity in Percentage of Cycles by Gemcitabine Group and Control Group*

	Gemcitabine (n = 1116 cycles)			Observation (n = 1092 cycles)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic						
Hemoglobin	27.9	0.6	0	3.3	0.1	0
Leukocytes	30.8	2.4	0	2.1	0.1	0
Platelets	6.4	0.5	0.3	1.0	0	0
Nonhematologic						
Nausea/vomiting	21.2	1.3	0	2.8	0.2	0
Diarrhea	9.0	0.9	0	5.1	0.4	0
Edema	8.9	0.4	0.1	0.4	0.1	0
Infection	3.9	0.4	0	1.7	0.3	0
Biochemical						
Alanine transaminase/aspartate transaminase	20.5	0.5	0.1	12.5	0.5	0.1
Bilirubin	1.2	0.1	0	2.1	0.1	0.1
Alkaline phosphatase	11.7	0.1	0	9.8	0.5	0

*The worst toxicity grade experienced by a patient during a cycle is presented. Every 4-weekly assessment period during the 24 weeks' duration of the study was counted as a cycle, whether or not treatment was given.

Table 3. Disease-Free and Overall Survival by Intent-to-Treat Analysis in the Total Population and in Patient Subgroups

	No. of Patients		Disease-Free Survival, Median (95% CI), mo			Overall Survival, Median, mo		
	Gemcitabine	Observation	Gemcitabine	Observation	P Value*	Gemcitabine	Observation	P Value*
All patients	179	175	13.4 (11.4-15.3)	6.9 (6.1-7.8)	<.001	22.1	20.2	.06
R0	145	148	13.1 (11.6-14.6)	7.3 (5.9-8.7)	<.001	21.7	20.8	.18
R1	34	27	15.8 (7.5-24.1)	5.5 (4.1-6.9)	<.001	22.1	14.1	.07
N ⁻	52	48	24.8 (6.8-42.7)	10.4 (6.4-14.3)	.003	34.0	27.6	.04
N ⁺	127	127	12.1 (10.7-13.4)	6.4 (5.7-7.2)	<.001	18.5	18.2	.44
T1-2	25	24	48.2 (0-96.8)	10.0 (4.4-15.5)	.02	50.2	27.6	.28
T3-4	154	151	12.9 (11.5-14.3)	6.7 (5.9-7.5)	<.001	20.5	19.1	.11

Abbreviation: CI, confidence interval.

*Log-rank test.

analysis, and for N⁺ patients both in the intent-to-treat (34.0 vs 27.6 months; $P=.04$) and the qualified analysis (51.8 vs 27.6 months; $P=.008$). For all other subgroups, the overall survival difference between groups failed to reach statistical significance in either analysis. However, the R1 and T1-2 subgroups were small in size.

Clinical Benefit and Quality of Life

The median Karnofsky performance status of the patients increased from 80% at baseline to 90% after 6 months in both treatment groups. The average body weight showed a slight increase over the course of treatment in the gemcitabine group and a slight decrease during the same time in the control group; the difference between the groups was significant from month 4 to month 6 ($P<.01$).

The average CA19-9 tumor marker levels increased, and the average CEA levels remained relatively stable in both groups with no significant differences between the groups. Quality of life as measured by the mean total Spitzer score improved similarly in both groups, from 1.4 prior to cycle 1, to 1.8 prior to cycle 6. There were no significant differences between the groups at any time point. The changes over time in the 5 dimensions of the Spitzer questionnaire, ie, activity, daily life, health, social relations, and future, largely paralleled the course of the total Spitzer score, again with no significant differences between the groups.

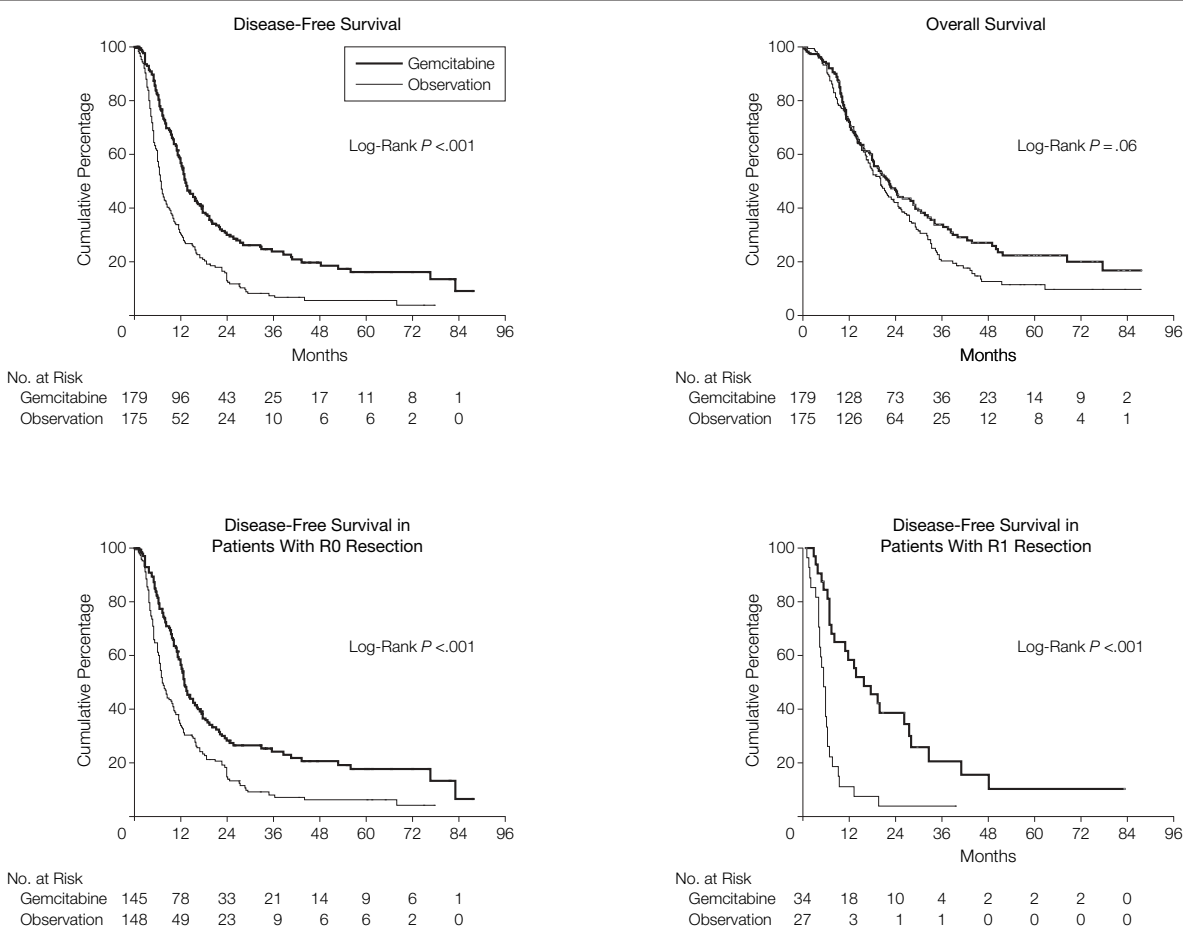
COMMENT

The primary end point analysis of this trial demonstrated that in accordance with our study hypothesis, 6 months of

adjuvant treatment with gemcitabine improved median disease-free survival significantly in patients with completely resected pancreatic cancer by more than 6 months compared with observation alone (13.4 vs 6.9 months, $P<.001$). With a median follow-up of 53 months, the disease-free survival analysis was based on a total number of 294 (83%) observed relapses among 354 randomized patients. The beneficial effect of adjuvant gemcitabine on disease-free survival was evident both in patients with R0 (13.1 vs 7.3 months; $P<.001$, log-rank) and R1 resection (15.8 vs 5.5 months; $P<.001$, log-rank).

Overall survival was not significantly different in the intent-to-treat analysis at the time of writing ($P=.061$), with 27% of all patients being still alive.

Figure 2. Disease-Free and Overall Survival (Intent-to-Treat Analysis)



Median survival times were 22.1 vs 20.2 months in the gemcitabine group and the control group, respectively. This relatively small difference in median survival may be explained by the fact that in accordance with German treatment standards, almost all patients in the control group received gemcitabine upon relapse, and some patients also received subsequent lines of chemotherapy, up to third-line. The separation of the survival curves increased with time, and estimated survival at 3 years was 34.0% in the gemcitabine group compared with 20.5% in the control group. At 5 years, approximately twice as many patients in the gemcitabine group compared with control are estimated to be alive (22.5 vs 11.5%). Therefore, it seems highly likely that the difference in overall survival between groups will become statistically significant with a longer follow-up and an increasing proportion of deceased patients.

Our qualified survival analysis was prespecified and designed to provide results that more closely reflect the "true" therapeutic potential of adjuvant gemcitabine in this setting. Therefore, we only included patients from the active group who received at least 1 full cycle (3 weekly doses) of gemcitabine, and patients from the control group who did not receive any cytotoxic agents or radiation therapy prior to relapse. All patient records were repeatedly and carefully reviewed, and patients from both groups were excluded from the analysis even if minor violations of the entry criteria were identified (Figure 1). As anticipated from this selection process (that is naturally not without some risk of bias), the advantage in disease-free survival and overall survival conferred by adjuvant gemcitabine vs observation alone was greater in the qualified compared with the intent-to-treat population and included a significant improvement in median overall survival (24.2 vs 20.5 months; $P=.02$).

CONKO-001 is the largest 2-group randomized trial of adjuvant chemotherapy in resected pancreatic cancer patients reported so far. The study had

a simple and straightforward design. Only 14 patients (7 in each group) out of a total of 368 enrolled patients had to be excluded from the intent-to-treat population due to major violations of the entry criteria. Patients were prospectively randomized into the study groups. Observation-only was chosen as control because no adjuvant chemotherapy or chemoradiation regimen had previously shown convincing results in randomized studies, let alone a recommended standard existing, at the time of study initiation. Gemcitabine was chosen as adjuvant treatment because it was, and still is considered the most active single agent in the treatment of locally advanced or metastatic pancreatic cancer. The distribution of patient baseline characteristics was nearly identical in the 2 groups, suggesting good comparability.

We are fully aware that our post-hoc subgroup analyses by resection, nodal, and T status may be flawed by small patient numbers, and we did not adjust P values for multiple comparisons. Moreover, classification of patients was not validated. There was no central or independent review of preoperative tumor staging or pathologic assessment of the surgical specimens in our study. Pancreatic resections were performed in hospitals of varying size and, presumably, surgical expertise. A large number of centers participated in the study, and approximately one third of all patients were enrolled by small community hospitals and oncology practices, each of which recruited no more than 1 to 3 patients. All this may have affected the reliability of the staging and pathology data. On the other hand, it is reasonable to assume that our study sample was representative of the patient population seen in routine clinical practice, and the quality of patient care may reflect the current standard in Germany.

It is all the more remarkable, therefore, that the beneficial effect of adjuvant gemcitabine on disease-free survival was consistent across all subgroups examined, and particularly impressive in the poor-prognosis sub-

groups R1, N⁺, and T3-4. Of note, median disease-free survival among N⁻ patients, ie, the subgroup with the lowest risk of relapse, was as short as 12 months in the control group, while median disease-free survival in the high-risk group of patients with R1 resection nearly tripled to reach 15.8 months after treatment with gemcitabine. This finding confirms the notion that pancreatic cancer is a systemic disease even at an early stage and further emphasizes the need for effective adjuvant chemotherapy.

Due to the lack of standardized histopathologic assessment of the resection specimens, it is likely that positive margins were not detected in at least some of the resection specimens classified as R0 in either group. Subgrouping of the patients by resection status was, however, reliable enough to reflect the improved prognosis following R0 compared with R1 resection: in the control group, median overall survival was 20.8 months (95% CI, 17.4-24.3) for the R0 and only 14.1 months (95% CI, 12.2-16.0) for the R1 subgroup. Remarkably, median overall survival for R0 and R1 patients was very similar in the gemcitabine group (21.7 months, 95% CI, 17.9-25.5; vs 22.1 months, 95% CI, 4.3-39.9, respectively).

The question as to whether adjuvant treatment of resected pancreatic cancer confers a long-term survival advantage has been a subject of controversy during the last 20 years. Most of the randomized trials compared adjuvant fluorouracil-based chemoradiation protocols with surgery alone. In the United States and Canada, chemoradiation has meanwhile been adopted as an adjuvant standard, based on a small study of the Gastrointestinal Tumor Study Group, which randomized patients to a split-course chemoradiation group with fluorouracil (21 patients) or observation (22 patients).¹⁷ Adjuvant chemotherapy alone, without radiation, was compared with observation in 3 randomized studies. Combination chemotherapy with fluorouracil, doxorubicin, and mitomycin

produced a significant advantage in median survival (23 vs 11 months; $P=.02$), but did not improve long-term survival.¹⁶ Patients with resected pancreatic cancer did not benefit from adjuvant mitomycin and fluorouracil or from cisplatin and fluorouracil in 2 Japanese studies.^{12,14}

Based on these data, the role of adjuvant fluorouracil given either alone or with radiation, to improve prognosis of patients with resected pancreatic cancer, remains questionable. Little support for the potential usefulness of this agent in the adjuvant setting comes from palliative trials of fluorouracil for advanced pancreatic cancer. It is well known from other tumors, including breast and colon cancer, that significant antitumor activity in advanced disease is mandatory for a cytotoxic single agent or combination to be effective as adjuvant treatment in early disease. In a large randomized trial of fluorouracil with or without cisplatin recently reported by Ducreux et al, the survival rates at 6 months were disappointingly low in both groups (28% with fluorouracil alone vs 38% with fluorouracil and cisplatin).²² With gemcitabine, 6-month survival rates were 50% or more in most randomized trials.^{19,23}

Gemcitabine has shown superior clinical benefit and improved median survival in a randomized comparison with fluorouracil in advanced pancreatic cancer¹⁹ and is now widely accepted as the palliative treatment standard.^{24,25} Based on the results of CONKO-001, gemcitabine offers promise to also become the new standard treatment in the adjuvant setting. This conclusion needs to be discussed primarily in the context of the most recent results of 2 large randomized phase 3 trials, ESPAC-1 and RTOG 9704. These trials have attracted considerable interest as they have added information as to the relative role of fluorouracil and gemcitabine in the adjuvant setting. In ESPAC-1, a total of 289 patients were randomly assigned, using a 2×2 factorial design, to receive either: (A) chemoradiotherapy alone (20 Gy over 2 weeks plus fluo-

uracil); (B) chemotherapy with fluorouracil alone (6 cycles of the Mayo Clinic schedule); (C) chemoradiotherapy followed by chemotherapy (both defined previously); or (D) neither treatment (observation). In accordance with the study design, 2 separate comparisons were performed: (1) chemotherapy (ie, chemotherapy alone or in addition to chemoradiotherapy) vs no chemotherapy (ie, chemoradiotherapy or observation), and (2) chemoradiotherapy (ie, chemoradiotherapy alone or chemoradiotherapy followed by chemotherapy) vs no chemoradiotherapy (ie, chemotherapy alone or observation). Mature results were reported after a median follow-up of 47 months, and the authors concluded that adjuvant radiation had a deleterious effect, possibly because it delayed sequential chemotherapy, while chemotherapy with fluorouracil had a significant beneficial effect.¹³

This study has been criticized for its complex design and, hence, the difficulties in interpreting the results. Indeed, given the marginal activity of fluorouracil in the palliative setting, the survival advantage obtained with adjuvant fluorouracil in ESPAC-1 appears very surprising. A statistical comparison of the 4 original groups based on the 2×2 randomization was not possible due to lack of adequate power. For example, median survival among the 75 patients randomized to fluorouracil chemotherapy was 21.6 months (95% CI, 14.2-22.5) compared with 16.9 months (95% CI, 12.3-24.8) for the 69 patients randomized to observation. Thus, 95% CIs were large and widely overlapping. Since disease-free survival as well as 3-year overall survival data were not reported, a comparison with the results of our study is not possible.

Preliminary results of RTOG 9704, a large randomized Gastrointestinal US Intergroup trial, were presented at the 2006 annual meeting of the American Society of Clinical Oncology.²⁶ This study included 442 eligible patients and was designed to determine if the addition of gemcitabine to adjuvant fluo-

uracil-based chemoradiotherapy improves survival in patients with gross complete resection of pancreatic cancer. Chemotherapy with either gemcitabine or fluorouracil was given over 3 weeks before and 12 weeks after chemoradiation that consisted of radiation therapy with fluorouracil as a radiosensitizer in both groups. In contrast to ESPAC-1, fluorouracil was given by continuous infusion in this trial. It was shown that in the subgroup of 381 patients with pancreatic head tumors, but not in the total study population that included patients with body or tail tumors, gemcitabine significantly improved overall survival (median, 20.6 vs 16.9 months; 3-year survival, 32% vs 21%; $P=.03$). Median disease-free survival was not improved (11.4 vs 10.1 months, $P=.10$). Interestingly, the 3-year survival rate of 21% found in the fluorouracil group of the RTOG trial is identical to that seen in the control group of our study.

Although comparing survival data across studies is problematic and the patients treated in CONKO-001 and the RTOG trial differed in some baseline characteristics, this finding appears to add further evidence to the assumption that the beneficial effect of adjuvant fluorouracil is small at best. Moreover, the toxicity in both treatment groups of the RTOG trial was substantial. In the gemcitabine group, grade 3 or 4 hematologic toxicity occurred in 58% of the patients and approximately 80% of the patients experienced any grade 3 or 4 toxicity. Clearly, mature results from this trial and perhaps additional comparative trials are needed to better substantiate the role of adjuvant chemoradiation with gemcitabine and fluorouracil and its efficacy and toxicity relative to gemcitabine alone.

The results of CONKO-001 indicate that adjuvant treatment with gemcitabine in the dose and schedule used has minimal toxicity, does not compromise quality of life, and offers a good, and currently perhaps the best, chance for prolonged disease-free survival in patients undergoing R0 or R1 resection for pancreatic cancer.

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