Original Paper

The Clinical Efficacy of Adjuvant Systemic Chemotherapy with Gemcitabine and NSC-631570 in Advanced Pancreatic Cancer

Frank Gansauge[1], Marco Ramadani[2], Michael Schwarz[1], Hans G Beger[1,3] Erkki Lotspeich[4], Bertram Poch[1]

[1]Center for Oncological, Endocrinological and Minimal-access Surgery, [2]Cabion Technologies [3]Pancreatic Cancer Research Group, University of Ulm, and [4]Army Hospital Department of Surgery, Ulm, Germany

Corresponding Author: Dr. Frank Gansauge, Center for Oncological Endocrinological and Minimal-access Surgery, Silcherstr. 36, 89231 Neu-Ulm, Germany Tel: +49 731 71576 0, Fax: +49 731 71576 251, E-mail: frank.gansauge@eurosurgery.de

ABSTRACT

Background/Aims: Recently we have shown that NSC-631570 (Ukrain) is a safe and effective drug in the treatment of unresectable pancreatic cancer. The aim of this study was to determine the effectiveness of the combined treatment with Gemcitabine and NSC-631570 in the adjuvant treatment of resected advanced pancreatic cancer.

Methodology: 30 patients received adjuvant chemotherapy following surgical resection for pancreatic cancer. Chemotherapy consisted of Gemcitabine according to the Burris-protocol with weekly infusions of 1000mg/sqm. Immediately following Gemcitabine infusion 20mg of NSC-631570 were administered intravenously over 15 minutes.

Results: WHO grade II toxicities were observed in 53%, no WHO grade III or IV toxicities occurred. In 80% of the patients recurrence of the disease was observed. The relapse-free survival time was 21.7 months. The actuarial survival rates were 86.7% after one year, 76.6% after two years, 46.7% after three years and 23.3% after five years. The median survival time according to Kaplan-Meier regression analysis was 33.8 months.

Conclusions: Adjuvant chemotherapy in advanced stages of pancreatic cancer using the combination of Gemcitabine and NSC-631570 is a safe treatment and seems to lead to a prolonged survival. Although further investigation is needed to confirm these results, the combined treatment of Gemcitabine and NSC-631570 is a promising therapy for the adjuvant treatment of resectable advanced pancreatic cancer.

KEY WORDS: AUTHOR please provide

INTRODUCTION

Ductal adenocarcinoma of the pancreas remains one of the most difficult cancers to treat with overall 5-year survival rates of only 0-4% (1) and a 5-year relative survival of 4%. Although 10-15% of patients undergo potentially curative resection of the tumor, with a low postoperative mortality rate, the median survival is only 10-18 months with 5-year survival of 17-24% (2). In patients with node-positive tumors the 5-year survival rate is even lower being less than 10% (3,4). An extensive lymph node dissection does not necessarily result in a favorable prognosis (5). In order to improve patient survival, development of adjuvant chemotherapeutic strategies in addition to surgery is mandatory.

In the palliative treatment of pancreatic cancer systemic chemotherapy using Gemcitabine is the standard first-line therapy (6,7). Recent studies have shown that also in the adjuvant treatment of pancreatic cancer using Gemcitabine has beneficial effects concerning the relapse-free survival as well as the overall survival (8), whereas radiochemotherapy using 5-FU as the chemotherapeutic agent did not lead to increased survival rates (9).

Recently we have shown that palliative systemic chemotherapy using Gemcitabine and NSC-631570 in unresectable pancreatic cancer increases median survival rates as compared to chemotherapy using Gemcitabine monotherapy (10). In the present study we investigated the use of Gemcitabine and NSC-631570 in the adjuvant situation in patients with advanced pancreatic cancer.

METHODOLOGY

Patients and Methods

From November 1999 to May 2002, 30 patients (14 female, 16 male) were included in this study. All patients underwent pancreatic cancer resection with curative intent for locally advanced pancreatic cancer. All patients gave informed consent. 8 Patients were classified UICC stage II, 22 patients were classified UICC stage III. The mean age was 62.3 years ranging from 31 to 78 years. In one patient a resection of the pancreatic tail was performed, 29 patients underwent pancreatic head resection (23 pylorus preserving partial duodenopancreatectomies, 6 partial duodenopan-

Hepato-Gastroenterology 2007; 54:917-920

TABLE 1 Side Effects in Patients with Pancreatic Cancer Treated with Gemcitabine and NSC-631570

	WHO I	WHO II	WHO III
Hematological	42%	29%	0%
Obstipation	3%	0%	0%
Nausea	15%	8%	0%
Diarrhea	17%	4%	0%
Fever	22%	12%	0%

TABLE 2 Pattern of Relapse and Metastazation in Patients with Pancreatic Cancer Adjuvantly Treated with Gemcitabine and NSC-631570

Site of relapse	Number of patients	Percent	Time after resection (months)
Local	**8/24**	**33%**	**23.3**
Liver	7/24	29%	16.7
Peritoneum	7/24	29%	23.7
Lymph nodes	7/24	29%	10.2
Lung	3/24	12.5%	34.2
Bone	2/24	16.7%	20.3

createctomies).

In all patients a R0 resection was performed. In addition an extensive lymph node resection was performed (11). Following resection 24 patients became tumor marker negative, and in 6 patients tumor marker CA19-9 did not return to normal values following resection. Adjuvant chemotherapy consisting of Gemcitabine and NSC-631570 was performed according to a recently published protocol (10) with a mean of 9.8 cycles (range 3-12 cycles). One cycle consisted of weekly infusions of Gemcitabine (1000mg/sqm) and 20mg of NSC-631570 for three weeks followed by one week without therapy. Toxicity was evaluated at every treatment, tumor marker CA19-9 was evaluated at every cycle. Every three months patients were reevaluated according to WHO-criteria, including chest X-ray, ultrasound of the abdomen and CT-scan of the upper abdomen during the first two years, followed by the same examinations every 6 months.

RESULTS

Clinical study: A mean number of 9.0 cycles (range 3-12 cycles) was applied. There were no drop outs due to serious side effects or interruption of the therapy by the patient. Actually 6 patients are alive more than 5 years following operation for pancreatic cancer without recurrence of the disease.

Complications related to chemotherapy: WHO Grade II toxicities were observed in 53% (**Table 1**). These toxicities were mainly due to hematological reasons. Grade III and grade IV complications were not observed. No skin rash, hair loss, severe fever or stomatitis occurred during the treatment period. Although the treatment of several patients was a little delayed at some time during this study period, chemotherapy was well tolerated and there were no life-threatening complications. Gastrointestinal bleeding as observed in the previously published study in palliative treatment of pancreatic cancer (10) did not occur.

Pattern of recurrence and relapse-free survival: In 24 out of the 30 patients, local recurrence or ***metastasation*** **(AUTHOR is this word correct?)** was observed. The sites of recurrences are shown in **Table 2**. Local recurrence was found in 8 out of these 24 patients. Peritoneal recurrence or recurrence in retroperitoneal lymph nodes was observed in 7 out of these 24 patients. Hepatic metastases were found in 7 patients. Interestingly 2 patients developed bone metastases which is rather rare in pancreatic cancer. Bone metastases especially occurred late following operation and adjuvant chemotherapy (38 and 30.4 months following resection).

In Kaplan-Meier analysis the median relapse-free survival time was 21.7 months (**Figure 1**). The relapse-free survival rates were 76.6% after one year, 50% after two years, 30% after three years and 20% after five years.

Survival: The actuarial survival rates were 86.7% after one year, 76.6% after two years, 46.7% after three years and 23.3% after five years. One patient developed recurrence of the disease 50 months follow-

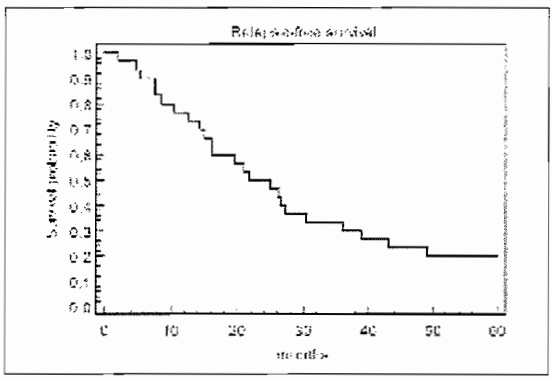


FIGURE 1 The disease-free interval. The disease-free interval following surgery for pancreatic cancer was 21.7 months.

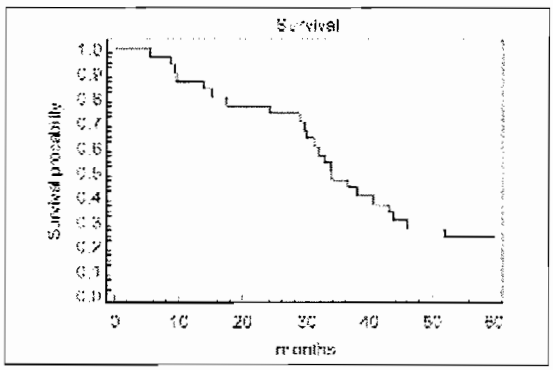


FIGURE 2 Median survival times according to Kaplan-Meier-regression analysis. The median survival time following surgery for pancreatic cancer was 33.8 months. One patient died 62 months following operation; six patients are still alive without recurrence of the disease.

ing operation and died 62 months after operation. The median survival time according to Kaplan-Meier regression analysis was 33.8 months **(Figure 2)**. Six patients (20%) are still alive without recurrence of the disease, more than 5 years after operation.

DISCUSSION

In advanced pancreatic cancer the lymph node status as well as the extension of the primary tumors are known to be important prognostic factors. Especially lymph node metastases have a negative impact on patients' survival following surgery (12-14). In our study we included only patients showing at least one of these risk factors. Other well known prognostic factors such as extra-pancreatic neural invasion (15) and portal vein involvement (16) were also frequently observed.

Gemcitabine is a promising new agent for the palliative treatment of pancreatic cancer with tolerable toxicity levels, a favorable antitumor activity, and relief of the symptoms related to this very aggressive kind of cancer (6,7). In recent studies the beneficial effect of Gemcitabine in the adjuvant treatment of pancreatic cancer patients following resection has been shown by several investigators (8,9). Recently we have shown that in the palliative treatment of pancreatic cancer the combined therapy with Gemcitabine and NSC-631570 is superior to the Gemcitabine monotherapy without increasing toxicity and side effects of the treatment (10). For this reason we combined adjuvant Gemcitabine treatment with NSC-631570. As in the palliative treatment addition of NSC-631570 to the Gemcitabine chemotherapy did not increase toxicity and all treatments were performed on an outpatient basis. Although 80% of the patients developed recurrence of the disease it is notable, that under this combined treatment the relapse-free survival was prolonged as compared to recently published studies (8,9,17). Even the pattern of recurrence of the disease was different to our observations. ***In our study we observed in two of the patients who developed recurrence bone metastases, which is probably due to the fact that this site of metastasation normally needs more time to develop and is covered by peritoneal or hepatic metastasation which leads to a fulminant progression of the disease before this metastasation site becomes clinically apparent*** **(AUTHOR please rephrase this sentence to clarify its meaning)**. This theory is supported by the observation that bone metastases occurred late after resection of the tumor and adjuvant chemotherapy. With regard to the survival times, 20% of the patients enrolled into this study were disease-free after five years and a median survival time according to Kaplan-Meier regression analysis of 33.8 months was observed. In comparison with other adjuvant chemotherapeutic or radio-chemotherapeutic regimens, the adjuvant treatment using Gemcitabine and NSC-631570 seems to increase postoperative survival times in these patients **(Table 3)**.

TABLE 3 Analysis of Different Adjuvant Therapies in Advanced Pancreatic Cancer

Author	Year	No. of patients	Therapy	Relapse-free survival	Median survival
Neoptolemos	2001	238	5-FU/FS	no data	19.7
Kurosaki	2004	16	Gemzar	16.8	20.4
Gansauge	2006	30	Gemzar/Ukrain	21.7	33.8

Although this monocentric pilot-study enrolled only a small number of patients without comparing different treatment modalities, the combination therapy of the both cytostatic agents Gemcitabine and NSC-631570 seems to be highly effective in the adjuvant treatment of resected pancreatic cancer and these data should be the basis for a randomized study comparing Gemcitabine monotherapy and the combination therapy of Gemcitabine and NSC-631570.

CONCLUSION

Adjuvant chemotherapy in advanced stages of pancreatic cancer using the combination of Gemcitabine and NSC-631570 is a safe treatment and seems to lead to a prolonged survival. Although further investigation is needed to confirm these results, the combined treatment of Gemcitabine and NSC-631570 is a promising therapy for the adjuvant treatment of resectable advanced pancreatic cancer.

REFERENCES

1 **Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP:** Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. Br J Surg 1995; 82:111-115.

2 **Nitecki SS, Sarr MG, Colby TV, van Heerden JA:** Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg 1995; 221:59-66.

3 **Cameron JL, Crist DW, Sitzmann JV, Hruban RH, Boitnott JK, Seidler AJ, Coleman J:** Factors influencing survival after pancreaticoduodenectomy for pancreatic cancer. Am J Surg 1991; 161:120-124.

4 **Baumel H, Huguier M, Manderscheid JC, Fabre JM, Houry S, Fagot H:** Results of resection for cancer of the exocrine pancreas: a study from the French Association of Surgery. Br J Surg 1994; 81:102-107.

5 **Kawarada Y, Das BC, Naganuma T, Isaji S:** Surgical treatment of pancreatic cancer. Does extended lymphadenectomy provide a better outcome? J Hepatobiliary Pancreat Surg 2001; 8:224-229.

6 **Moore M:** Activity of gemcitabine in patients with advanced pancreatic carcinoma. A review. Cancer 1996; 78:633-638.

7 **Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD:** Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15:2403-2413.

8 **Kurosaki I, Hatakeyama K:** The clinical efficacy of adjuvant systemic chemotherapy with gemcitabine in node-posi-

tive pancreatic cancer. Hepatogastroenterology 2004; 51:634-637.

9 **Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Buchler MW:** Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001; 358:1576-1585.

10 **Gansauge F, Ramadani M, Pressmar J, Gansauge S, Muehling B, Stecker K, Cammerer G, Leder G, Beger HG:** NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial. Langenbecks Arch Surg 2002; 386:570-574.

11 **Birk D, Beger HG:** Lymph-node dissection in pancreatic cancer - what are the facts? Langenbecks Arch Surg 1999; 384:158-166

12 **Beger HG, Rau B, Gansauge F, Poch B, Link KH:** Treatment of pancreatic cancer: challenge of the facts. World J Surg 2003; 27:1075-1084.

13 **Delcore R, Rodriguez FJ, Forster J, Hermreck AS, Thomas JH:** Significance of lymph node metastases in patients with pancreatic cancer undergoing curative resection. Am J Surg 1996; 172:463-468.

14 **Lygidakis NJ, Papadopoulou P:** Pancreatic head carcinoma: is pancreatic resection indicated for patients with stage III pancreatic duct cancer? Hepatogastroenterology 1995; 42:587-596.

15 **Nagakawa T, Kayahara M, Ohta T, Ueno K, Konishi I, Miyazaki I:** Patterns of neural and plexus invasion of human pancreatic cancer and experimental cancer. Int J Pancreatol 1991; 10:113-119.

16 **Ishikawa O:** Surgical technique, curability and postoperative quality of life in an extended pancreatectomy for adenocarcinoma of the pancreas. Hepatogastroenterology 1996; 43:320-325.

17 **Kosuge T, Kiuchi T, Mukai K, Kakizoe T:** A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Jpn J Clin Oncol 2006; 36:159-165.

AUTHOR PLEASE REPHRASE HIGHLIGHTED SENTENCE PLEASE PROVIDE KEY WORDS AND PLEASE CHECK HIGHLIGHTED WORDS IN THE TEXT

Langenbeck's Arch Surg (2002) 386:570–574
DOI 10.1007/s00423-001-0267-5

ORIGINAL ARTICLE

Frank Gansauge
Marco Ramadani
Jochen Pressmar
Susanne Gansauge
Bernd Muehling
Kerstin Stecker
Gregor Cammerer
Gerd Leder
Hans G. Beger

NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer

Results of a phase II trial

Received: 10 September 2001
Accepted: 27 November 2001
Published online: 13 February 2002

F. Gansauge · M. Ramadani · J. Pressmar
B. Muehling · K. Stecker · G. Cammerer
G. Leder · H.G. Beger (✉)
Department of General Surgery,
University of Ulm, Germany
e-mail: hans.beger@medizin.uni-ulm.de
Tel.: +49-731-50026780
Fax: +49-731-50026787

H.G. Beger
Professor for Surgery, University of Ulm,
Steinhoevelstrasse 9, 89075 Ulm, Germany

F. Gansauge · M. Ramadani · S. Gansauge
H.G. Beger
bio.*Venture* Technologies,
Rechbergweg 31, 89075 Ulm, Germany

M. Ramadani · S. Gansauge
Division of Molecular Oncology,
Department of General Surgery,
University of Ulm, Germany

Abstract *Background*: NSC-631570 (Ukrain) is a semisynthetic compound of thiophosphoric acid and the alkaloid chelidonine from the plant *Chelidonium majus*. It has been used in complementary herbal medicine for more than 20 years for the treatment of benign and malignant tumors. *Patients/methods:* Between August 1999 and June 2001, 90 patients with histologically proven unresectable pancreatic cancer were randomized in a monocentric, controlled, randomized study. Patients in arm A received 1000 mg gemcitabine/m^2, those in arm B received 20 mg NSC-631570, and those in arm C received 1000 mg gemcitabine/m^2 followed by 20 mg NSC-631570 weekly. End point of the study was overall survival. *Results:* In all three arms therapy was well tolerated and toxicity was moderate. At the first re-evaluation in arm A 32%, in arm B 75%, and in arm C 82% showed no change or partial remission according to WHO criteria (arm A versus arm B: $P<0.01$, arm A versus arm C: $P<0.001$). Median survival according to Kaplan-Meier analysis was in arm A 5.2 months, in arm B 7.9 months, and in arm C 10.4 months (arm A versus arm B: $P<0.01$, arm A versus arm C: $P<0.01$). Actuarial survival rates after 6 months were 26%, 65% and 74% in arms A B and C, respectively (arm A versus arm B: $P<0.05$, arm A versus arm C $P<0.01$). *Conclusion*: We could show that in unresectable advanced pancreatic cancer, NSC-631570 alone and in combination with gemcitabine nearly doubled the median survival times in patients suffering from advanced pancreatic cancer.

Keywords Pancreatic cancer · Chemotherapy · Gemcitabine · NSC-631570 · Ukrain

Introduction

So far, no highly effective treatment for advanced pancreatic cancer has been established. During the past years, gemcitabine was found to have a positive influence on the quality of life in pancreatic cancer patients palliatively treated with weekly infusions of gemcitabine; however, median survival times in patients treated with gemcitabine were only marginally prolonged [1]. Protocols using combinations of gemcitabine with 5-FU with or without folinic acid or combinations of gemcitabine and cisplatinium have prolonged median survival up to 8.3 months [2, 3, 4]. Additional radiation therapy in combination with mitomycin C and gemcitabine did not significantly improve survival [5]. In our clinic we used intra-arterial infusions of the celiac trunk using 5-FU, mitoxantrone and cisplatinum and observed an improvement in survival; however, this treatment of regional chemotherapy is associated with long periods of hospitalization [6].

Several plant-derived drugs are used in medical oncology. The greater celandine (*Chelidonium majus* L.) is a member of the Papaveraceae family and is a common weed in Europe and Western Asia [7]. For many centu-

ries the plant has been used in the therapy of warts, skin cancers, and liver and gallbladder diseases, and the major component of the wide variety of alkaloids found in this plant is chelidonine [8]. NSC-631570 (Ukrain) is a semisynthetic compound of thiotepa and the alkaloid chelidonine from the plant *Chelidonium majus*. NSC-631570 is thought to consist of 1 molecule thiophosphoric acid (thiotepa) conjugated to 3 molecules of chelidonine. It has been used in alternative medicine as an anticancer drug for more than 20 years without knowledge of the mechanism of its action. However, several promising case reports exist on the antitumoral effects of NSC-631570 in cancer patients [9, 10, 11, 12].

The aim of this study was to evaluate the clinical use of this plant-derived drug by means of intravenous therapy in the treatment of unresectable, highly advanced pancreatic cancer in a monocentric, controlled, randomized study.

Patients and methods

Monocentric, controlled, randomized study

Between August 1999 and June 2001, a total of 90 patients were recruited into the prospective, controlled, monocentric, randomized study. The study protocol was approved by the local ethics committee. Gemcitabine was supplied by Lilly (Giessen, Germany). NSC-631570 was generously provided by Nowicky Pharma (Vienna, Austria). Inclusion criteria were histologically proven unresectable adenocarcinoma of the pancreas. Exclusion criteria were age below 18 years, pregnancy or lack of contraception, other cancer diseases, viral infection with hepatitis B or C or HIV, immunosuppressive therapy, or diseases of the central nervous system. All patients gave informed consent to participation in the study prior to treatment. Therapy was reduced by 20% in cases of WHO grade II toxicities; in cases of WHO grade III toxicities therapy was interrupted until toxicity had normalized and was then continued with a dose reduction of 20%. In arm A, 30 patients received 1000 mg gemcitabine/m² weekly, according to the protocol recently published by Burris [1] (first cycle: 7 weeks of therapy, 1 week of rest; 2nd–12th cycles: 3 weeks of therapy, 1 week of rest). In arm B, 30 patients received 20 mg NSC-631570 weekly (first cycle: 7 weeks of therapy, 1 week of rest; 2nd–12th cycles: 3 weeks of therapy, 1 week of rest), and in arm C, 30 patients received 1000 mg gemcitabine/m² followed by 20 mg NSC-631570 weekly (first cycle: 7 weeks of therapy, 1 week of rest; 2nd–12th cycles: 3 weeks of therapy, 1 week of rest). In arms B and C in the first week of the first cycle, NSC-631570 was administered during the first 5 days at a daily dose of 20 mg per day. In all three arms, most of the patients received supplementary vitamins, especially vitamin C. During the first week of therapy the patients were treated as in-house patients; the following therapies were performed in the out-patient department. After 3, 6, 9, and 12 months, patients were re-evaluated according to WHO criteria, including chest X-ray, ultrasound of the abdomen and CT scan of the upper abdomen. Quality of life was assessed by the EORTC-QLQ-C30 Version 3.0. Patients who died prior to the first re-evaluation were considered PD (progressive disease). Tumor marker CA19–9 was evaluated at every treatment. Tumor marker response at the first restaging examination at 3 months was defined as follows: complete response (CR) = normalization of CA19–9 for more than 4 weeks, partial response (PR) = reduction of CA19–9 by more than 50% for 4 weeks, no change (NC) = no reduction >50% or elevation >50%, and progressive disease (PD) = elevation of CA19–9 by more than 50%. At each application toxicity and side effects were evaluated. The patients' characteristics are shown in Table 1. In each arm, 30 patients had been randomized.

Table 1 Patients receiving palliative chemotherapy. *UICC* Union Internationale Contra la Cancrum (International Union Against Cancer)

	Arm A Gemcitabine	Arm B NSC-631570	Arm C NSC-631570/gemcitabine
Number of patients	30	30	30
Mean age (range)	63.8 (53–79)	60.6 (40–80)	58.2 (22–74)
Sex			
Female	8	14	11
Male	22	16	19
Mean number of cycles (SD)	3.8 (3.1)	5.6 (3.9)	6.8 (3.9)*
UICC stage			
Stage 3	1	0	1
Stage 4a	12	13	7
Stage 4b	17	17	22
Recurrence	5	7	6
Metastases			
Hepatic	11	9	9
Peritoneal	5	5	5
Hepatic + peritoneal	1	5	8
Pulmonal	1	0	0
Other therapies prior to randomization			
Chemotherapy	1	1	3
Radiochemotherapy	1	4	2
Drop outs	2	2	2

*Significant as compared to arm A ($P<0.005$)

Table 2 Side effects in palliatively treated pancreatic cancer patients

	Gemcitabine Arm A			NSC-631570 Arm B			NSC-631570/gemcitabine Arm C		
	WHO I	WHO II	WHO III	WHO I	WHO II	WHO III	WHO I	WHO II	WHO III
Hematological	46%	13%	12%	25%	7%	11%	43%	32%	10%
Obstipation	0%	27%	0%	3%	3%	2%	3%	3%	1%
Nausea	9%	33%	11%	16%	3%	3%	18%	6%	3%
Diarrhea	18%	9%	2%	14%	10%	1%	16%	5%	0%
Fever	13%	9%	0%	22%	20%	0%	18%	16%	0%
Tumor bleeding		0%			7%			7%	

Results

Clinical study

In the gemcitabine monotherapy arm 25/30 patients had died, 2/30 patients had interrupted therapy and 3/30 patients are still under therapy. In the patients who finished therapy, a mean number of 3.8 cycles (SD: 3.1, ranging from 1 to 12 cycles) were applied. In the NSC-631570-monotherapy arm, 12/30 patients had died, 3/30 patients are alive after 12 cycles, 2/30 patients had interrupted therapy, and 13/30 patients are still under therapy. In the patients who finished therapy, a mean number of 5.6 cycles (SD: 3.9, ranging from 1 to 12 cycles) were applied. In the gemcitabine/NSC-631570 arm, 19/30 patients had died, 2/30 patients had interrupted therapy, 2/30 patients are alive after 12 cycles of therapy, and 7/30 patients are still under therapy. Compared with the gemcitabine monotherapy arm, significantly more cycles were applied in the gemcitabine/NSC-631570 arm (3.8 versus 6.8 cycles, $P<0.005$).

Side effects

In all three arms therapy was well tolerated and no severe side effects occurred. In no patient was it necessary to stop the therapy because of harmful side effects. In arm A nausea seemed to be more frequent than in arm B and arm C ($P<0.05$), whereas in arm B and arm C fever was observed more frequently ($P<0.05$). In arm C (gemcitabine plus NSC-631570) hematological toxicities WHO II occurred with significantly more frequency than in arm A and arm B ($P<0.05$). Increases in liver enzymes occurred in all three arms at the same frequency and were related to stent occlusion or disease progression of hepatic metastases. In four patients tumor bleeding occurred (two patients in arm B, two patients in arm C), which were treated by angiographic intervention. The side effects are shown in Table 2.

Quality of life

Quality of life was assessed by the EORTC-QLQ-C30 questionnaire prior to the beginning of treatment, and then every 3 months. In all three therapy arms no significant differences were observed between the start of the therapy and after 3 months concerning the first 28 questions. With regard to the last two questions concerning the self-estimation of the health status (question 29) and the self-estimation of the quality of life status (question 30), a significant improvement was noted in arm A and arm C (Fig. 1).

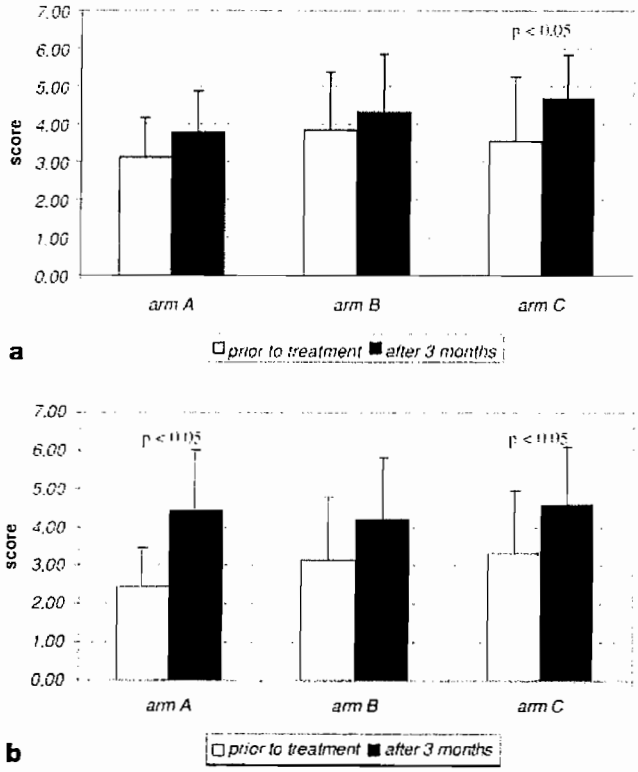


Fig. 1 Self-estimation of the health status (**a**) and the quality of life status (**b**) in palliatively treated pancreatic cancer patients prior to treatment and after 3 months of therapy. **a** With regard to the self-estimation of the health status a significant difference was observed in arm C, and **b** with regard to the self-estimation of the quality of life status a significant improvement was observed in arm A and arm C

Table 3 Response and survival in palliatively treated pancreatic cancer patients

	Arm A Gemcitabine	Arm B NSC-631570	Arm C NSC-631570 / gemcitabine
Tumor marker response			
Complete response	1/15	0/15	1/20
Partial response	5/15	4/15	7/20
No change	5/15	5/15	9/20
Progressive disease	4/15	5/15	3/20
Response after 3 months			
Complete response	0/28	0/20	0/28
Partial response	1/28	2/20	6/28
No change	8/28	13/20	17/28
Progressive disease	19/28	5/20	5/28
CR+PR+NC versus PD	9/19	15/5**	23/5***
Survival			
Survival rate (6 months)	26%	65%*	74%**
Survival rate (9 months)	13%	40%	56%**
Survival rate (12 months)	13%	29%	32%
Median survival (months)	5.2	7.9**	10.4**

*$P<0.05$ as compared to gemcitabine Monotherapy (arm A)
**$P<0.01$ as compared to gemcitabine Monotherapy (arm A)
***$P<0.001$ as compared to gemcitabine Monotherapy (arm A)

Response and survival

In all three groups the tumor marker response at the first restaging examination was comparable. According to the CA19–9 levels, disease was only progressive in 27%, 33% and 15% of the patients in arm A B and C, respectively. However, it has to be noted that only patients that had elevated CA19–9 serum levels and patients who underwent re-examination were evaluated, whereas patients who did not have elevated CA19–9 serum levels and patients who died prior to the first re-examination were not evaluated.

According to WHO criteria, patients were examined after 3 months of therapy. In both arm A and arm C two patients had stopped therapy prior to the first re-evaluation; in arm B one patient had stopped therapy and nine patients are under therapy without having reached the third month of therapy. No case of complete response according to CT scan was observed. In arm B and arm C significantly more patients showed partial response or no

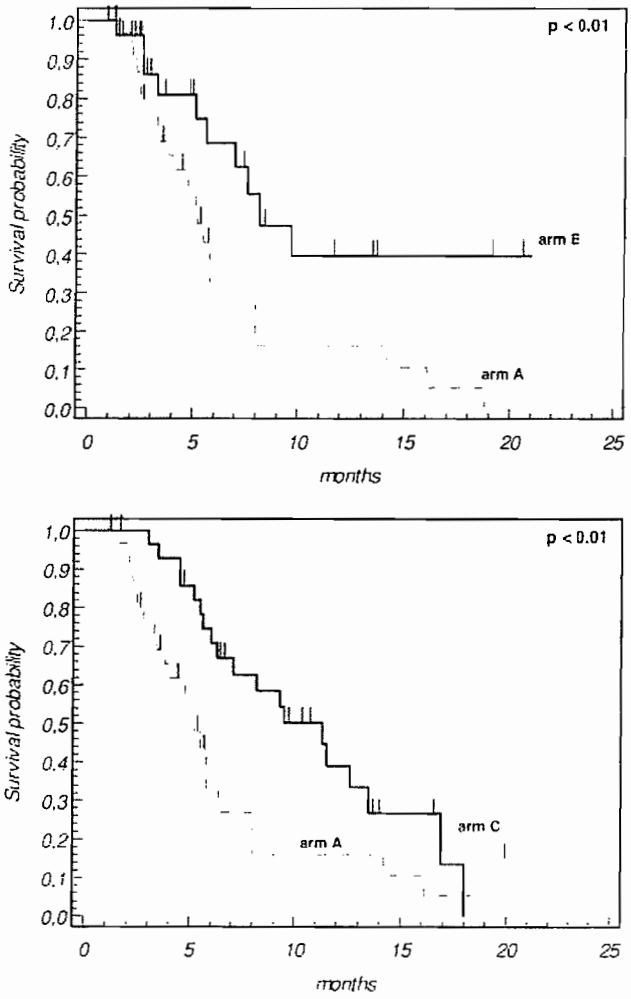


Fig. 2a,b Kaplan-Meier survival curves of advanced pancreatic cancer patients palliatively treated according to arm A, arm B, or arm C. **a** Patients who received NSC-631570 monotherapy (arm A, *solid line*) lived significantly longer as compared to patients treated with gemcitabine monotherapy (arm A, *dashed line*). Median survival times were arm A 5.2 months, arm B 7.9 months ($P<0.01$). **b** Patients who received NSC-631570 plus gemcitabine (arm C, *solid line*) lived significantly longer than patients with gemcitabine monotherapy (arm A, *dashed line*). Median survival times in arm C were 10.4 months ($P<0.01$). No statistically significant difference was found between median survival times in arm B and arm C

change after 3 months of therapy as compared to arm A (PR + NC: arm A 32%, arm B 75%, arm C 82%; arm A versus arm B: $P<0.01$; arm A versus arm C: $P<0.001$, chi-squared test) (Table 3).

Regarding actuarial survival rates and median survival times, patients in arm B and arm C lived significantly longer than patients in arm A. The actuarial survival rates after 6 months were in arm A 26%, in arm B 65%, and in arm C 74% (arm A versus arm B: $P<0.05$; arm A versus arm C: $P<0.01$; arm B versus arm C: not significant). Even after 9 months the actuarial survival in arm C was still significant as compared to arm A (56% versus 13%, $P<0.01$) (Table 3). These increased survival rates were also reflected in the median survival times according to Kaplan-Meier regression analysis. The median survival rate was significantly higher in arm B and arm C (7.85 months and 10.4 months) as compared to arm A (5.15 months, $P<0.01$ and $P<0.01$, respectively) (Table 3, Fig. 2).

Discussion

Since NSC-631570 has been used in a wide variety of cancers and has been described as a potent anticancer drug with minimal side effects, we performed a phase II study in unresectable advanced pancreatic cancer patients. In this controlled, randomized study, patients were treated either with gemcitabine, which is the most commonly used treatment in this disease, or with NSC-631570 or with gemcitabine plus NSC-631570. In the gemcitabine monotherapy arm (arm A) our findings were very similar to the data published by Burris and colleagues – that gemcitabine led to an increase in the quality of life and to a marginal increase in median survival times [1], whereas in the NSC-631570 monotherapy arm (arm B) only a statistically insignificant increase in the quality of life was observed. A combination of the two also led to an increase in the quality of life. Regarding the side effects, all three arms showed moderate side effects. It is noteworthy that in both the arms containing NSC-631570, in two cases tumor-bleeding into the duodenum occurred, which had to be treated angiographically. Very recently, cases of acute hepatitis under the treatment with plant extracts of greater celandine have been reported [13]. In our study we observed in all three arms several times cholangitis with increases in liver enzymes; however, in all cases an incrustation of a stent or occlusion of the common bile duct by tumor masses turned out to be the reason. Interestingly, median survival times were significantly longer in both arms containing NSC-631570 (arm B and arm C) as compared to the gemcitabine monotherapy arm (arm A), suggesting that NSC-631570 acts as a potent drug in the treatment of unresectable advanced pancreatic cancer.

In conclusion, we were able to show that in unresectable advanced pancreatic cancer, and in combination with gemcitabine, NSC-631570 nearly doubled the median survival times in these patients. However, since side effects such as tumor bleeding occurred under the treatment with NSC-631570, cancer treatment using this potent drug should be performed under medical control.

References

1. Burris H, Moore M, Andersen J, Green M, Rothenberg M, Modiano M, Cripps M, Portenoy R, Storniolo A, Tarassoff P, et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
2. Oettle H, Arning M, Pelzer U, Arnold D, Stroszczynski C, Langrehr J, Reitzig P, Kindler M, Herrenberger J, Musch R, et al (2000) A phase II trial of gemcitabine in combination with 5-fluorouracil (24-hour) and folinic acid in patients with chemonaive advanced pancreatic cancer. Ann Oncol 11:1267–1272
3. Kurtz J, Kohser F, Negrier S, Trillet Lenoir V, Walter S, Limacher J, Untereiner M, Kayitalire L, Jaeck D, Dufour P (2000) Gemcitabine and protracted 5-FU for advanced pancreatic cancer. A phase II study. Hepatogastroenterology 47:1450–1453
4. Heinemann V (2001) Gemcitabine: progress in the treatment of pancreatic cancer. Oncology 60:8–18
5. Kornek G, Potter R, Selzer E, Schratter A, Ulrich Pur H, Rogy M, Kraus G, Scheithauer W (2001) Combined radiochemotherapy of locally advanced unresectable pancreatic adenocarcinoma with mitomycin C plus 24-hour continuous infusional gemcitabine. Int J Radiat Oncol Biol Phys 49:665–671
6. Gansauge F, Link K, Rilinger N, Kunz R, Beger H (1995) Regionale Chemotherapie beim fortgeschrittenen Pankreaskarzinom. [Regional chemotherapy in advanced pancreatic carcinoma]. Med Klin 90:501–505
7. Colombo ML, Bosisio E (1996) Pharmacological activities of Chelidonium majus L. (Papaveraceae). Pharmacol Res 33:127–134
8. Kreitmeir H. (1950) Chelidonium majus L. – das Schöllkraut. Pharmazie 5 85–88
9. Vyas JJ, Jain VK (1996) Ukrain treatment in carcinoma of the oesophagus (case report). Drugs Exp Clin Res 22:267–269
10. Lohninger A, Korsh OB, Melnyk A (1996) Combined therapy with Ukrain and chemotherapy in ovarian cancer (case report). Drugs Exp Clin Res 22:259–262
11. Kadan P, Korsh OB, Melnyk A (1996) Ukrain therapy of recurrent breast cancer with lung metastases (case report). Drugs Exp Clin Res 22:243–245
12. Hamler F, Hiesmayr W, Korsh OB, Melnyk A. (1996) Ukrain monotherapy in malignant melanoma (case report). Drugs Exp Clin Res 22:235–237
13. Benninger J, Schneider H, Schuppan D, Kirchner T, Hahn E (1999) Acute hepatitis induced by greater celandine (Chelidonium majus). Gastroenterology 117:1234–1237

8. November 22.2002

Schweizer Zeitschrift für Hausarztmedizin ■ Revue suisse de médecine de premier recours ■ Rivista Svizzera della Medicina di Famiglia

ARS MEDICI

Beruf, Praxis, Politik, Gesellschaft

FMP: Et voilà les pierres d'achoppement en détails !

Medizin

Osteoporose und Frakturrisiko

Ukrain beim fortgeschrittenen Pankreaskarzinom

Die postpartale Depression

Moderne Aspekte der Fibromyalgie

Der ideale Laufschuh

Folsäuremangel mit Folgen

Offizielles Organ der
Ärzte mit Patientenapotheke (APA)

Offizielles Organ / Organe officiel
Foederatio Medicorum Practicorum /

Ukrain beim fortgeschrittenen Pankreaskarzinom

Viel versprechende Ergebnisse einer randomisierten und kontrollierten Phase-II-Studie

F. GANSAUGE, M. RAMADANI, HANS G. BEGER

Das Pankreaskarzinom ist ein sehr aggressiver Tumor, der selten kurabel ist. Die Therapie ist oft rein palliativ. Mit dem Chelidoninderivat Ukrain sollen hierbei erstaunliche Erfolge möglich sein, doch mangelt es bislang an zuverlässigen Daten. In der nachfolgend vorgestellten Studie an der Universitätsklinik Ulm wurde Ukrain erstmals unter kontrollierten Bedingungen getestet. [illegible]

Hintergrund

Das humane Pankreaskarzinom gehört immer noch zu den Tumorerkrankungen mit einer der schlechtesten Prognosen. Trotz verbesserter diagnostischer Strategien konnte die Anzahl an Krebserkrankungen der Bauchspeicheldrüse, die im Frühstadium entdeckt werden, bisher nur minimal erhöht werden. Die chirurgische Entfernung des Tumors stellt immer noch die einzige potenziell kurative Behandlung dar. Jedoch wird nur bei lediglich 5 bis 22 Prozent der Patienten die Erkrankung in einem Stadium diagnostiziert, in dem eine operative Entfernung des Tumors durchgeführt werden kann (1–4). Dies liegt vor allem an unspezifischen Symptomen, die im Frühstadium der Erkrankung auftreten. Doch selbst bei den Patienten, bei denen der Tumor vollkommen entfernt werden konnte, kommt es in der überwiegenden Mehrzahl zu einem Wiederauftreten des Tumors in Form eines Lokalrezidivs und/oder Lebermetastasen. Die mittlere Überlebenszeit bei Patienten, bei denen der Tumor mit kurativem Ziel reseziert wurde, beträgt selten mehr als 2,5 Jahre und die 5-Jahres-Überlebensrate im Gesamtkollektiv aller Erkrankten liegt unter 5 Prozent (1; 5–7).

Patienten, die aufgrund eines ausgedehnten Lokalbefundes oder des Vorhandenseins von Metastasen nicht von einer operativen Therapie profitieren, sind auf eine adäquate palliative Therapie angewiesen. Ziele einer solchen Therapie sind neben der Verbesserung der Prognose vor allem der Erhalt der Lebensqualität und die Linderung tumorbedingter Beschwerden wie Schmerzen, Verdauungsstörungen, Kräfteverfall sowie die Behandlung der Gelbsucht und eine adäquate Blutzuckereinstellung. In den Vereinigten Staaten beschränkt sich derzeit die Therapie beim fortgeschrittenen Pankreaskarzinom auf eine supportive Therapie im Sinne einer ausreichenden Analgesie und Linderung akuter Beschwerden (best supportive care). In Europa hat sich die palliative Chemotherapie mit Gemcitabine als «Quasistandardtherapie» durchgesetzt, da sie bei geringen Nebenwirkungen zu einer

Merksätze

Zur palliativen Therapie des Pankreaskarzinoms wird in Europa zumeist Gemcitabine eingesetzt, mit dem sich die Lebensqualität verbessern lässt, kaum dagegen die Lebenserwartung.

Ukrain ist ein bislang schlecht untersuchtes halbsynthetisches Chelidoninderivat, dessen zytostatische Wirkung auf Tumorzellen inzwischen charakterisiert werden konnte.

Im Rahmen einer randomisierten Studie wurden 90 Patienten mit fortgeschrittenem Pankreaskarzinom an der Tagesklinik der Chirurgischen Universitätsklinik Ulm behandelt. Sie erhielten entweder eine Monotherapie mit Gemcitabine und Ukrain oder eine Kombination beider Medikamente.

Ergebnisse: Nach 6 Monaten lebten unter Gemcitabine nur noch 26 Prozent der Patienten, unter Ukrain noch 65 Prozent und unter der Kombinationstherapie noch 74 Prozent. Nach 12 Monaten war kein Unterschied zwischen den Behandlungsgruppen mehr erkennbar. Die mittlere Überlebenszeit betrug unter Gemcitabine 5,2 Monate, unter Ukrain 7,9 Monate und unter der Kombinationstherapie 10,4 Monate.

Ukrain erwies sich als relativ gut verträglich. Hämatologische und gastrointestinale Nebenwirkungen sowie leichter Blutdruckabfall sind am ehesten zu erwarten.

Die Studienautoren halten eine weitere Evaluierung von Ukrain für gerechtfertigt, zumal die Patienten auch ihre Lebensqualität verbessert sahen.

Ukrain beim fortgeschrittenen Pankreaskarzinom

Tabelle 1: **Patientencharakteristika**

	Arm A Gemcitabine	Arm B NSC-631570	Arm C NSC-631570/Gemcitabine
Anzahl randomisierter Patienten	30	30	30
Medianes Alter (von – bis)	63,8 (53–79)	60,6 (40–80)	58,2 (22–74)
Geschlecht			
Weiblich	8	14	11
Männlich	22	16	19
UICC-Stadium			
Stadium 3	1	0	1
Stadium 4a	12	13	7
Stadium 4b	17	17	22
Rezidiv	5	7	6
Metastasen	60% (18/30)	63,3% (19/30)	73,3% (22/30)
Lebermetastasen	11	9	9
Peritonealkarzinose	5	5	5
Lebermetastasen + Peritonealkarzinose	1	5	8
Lungenmetastasen	1	0	0
Vorangegangene Therapien			
Chemotherapie	1	1	3
Radiochemotherapie	1	4	2
Drop-outs	2	2	2

Im Rahmen einer randomisierten, kontrollierten, monozentrischen Phase-II-Studie wurden insgesamt 90 Patienten behandelt. Bei allen 90 Patienten handelte es sich um Patienten mit einem histologisch gesicherten und weit fortgeschrittenen Pankreaskarzinom.

Verbesserung der Lebensqualität führt, den Verbrauch an Analgetika reduzieren und zu einer marginalen Verbesserung der mittleren Überlebenszeit von knapp über 4 Monaten auf knapp über 5 Monate führen kann (8). Dieses Therapieschema kann ambulant durchgeführt werden und vermeidet unerwünschte Hospitalisierung der Patienten zur Therapie. Durch aggressivere Chemotherapie-Regime konnte in mehreren Studien zwar eine etwas ausgeprägtere Verlängerung der Überlebenszeit erreicht werden, jedoch verlangen diese Therapieschemata eine längere Klinikverweildauer für die Patienten und bringen teilweise erheblich stärkere Nebenwirkungen mit sich, was wiederum zu einer erhöhten Rate von unerwünschten Klinikaufenthalten führt (9–11). Eine ambulant durchführbare und gut verträgliche Therapie für das humane Pankreaskarzinom, die zu einer deutlichen Verlängerung der medianen Überlebenszeit unter Erhalt der Lebensqualität ohne unnötige zusätzliche Klinikaufenthalte führt, würde deshalb einen grossen medizinischen Fortschritt bedeuten und die Perspektive von Patienten mit dieser sehr aggressiven Erkrankung wenigstens etwas verbessern.

Konzeption der Ukrain-Studie

Im Rahmen eines dreijährigen Forschungsprojektes, dass sich mit dem molekularen Wirkungsmechanismus des halbsynthetischen Chelidoninderivats Ukrain auf Bauchspeicheldrüsenkrebszellen beschäftigte, konnten Forscher der Abteilung Allgemeinchirurgie der Universität Ulm die Wirkung von Ukrain auf verschiedenste Tumorzellarten im Labor genau charakterisieren und zeigen, dass es sich bei Ukrain um eine zytostatisch wirkende Substanz handelt, die Tumorzellen direkt schädigt und zu deren Absterben führt (12). Aufgrund der erlangten Erkenntnisse wurde nach Zustimmung der Ethikkommission und Registrierung bei den entsprechenden öffentlichen Stellen eine klinische Studie zum Einsatz von Ukrain beim fortgeschrittenen Pankreaskarzinom initiiert. Im Rahmen dieser randomisierten Studie wurden insgesamt 90 Patienten ambulant in der Tagesklinik der Chirurgischen Universitätsklinik Ulm behandelt. 30 Patienten wurden nach dem Standardprotokoll mit 1000 mg/m² Körperoberfläche Gemcitabine pro Woche, 30 Patienten wurden mit einer Absolutdosis von 20 mg Ukrain pro Woche und 30 Patienten mit einer Kombination aus Gemcitabine und Ukrain behandelt (Dosis jeweils analog der Monotherapieprotokolle). Bei allen 90 Patienten handelte es sich um Patienten mit einem histologisch gesicherten und weit fortgeschrittenen Pankreaskarzinom (*Tabelle 1*). Patienten mit einem gesicherten Lokalrezidiv oder Progression unter anderen

Ukrain beim fortgeschrittenen Pankreaskarzinom

Tabelle 2: **Nebenwirkungen**

	Gemcitabine Arm A			Ukrain Arm B			Ukrain/Gemcitabine Arm C		
Nebenwirkungsgrad nach WHO	WHO I	WHO II	WHO III	WHO I	WHO II	WHO III	WHO I	WHO II	WHO III
Hämatologisch	46%	13%	12%	25%	7%	11%	43%	32%	10%
Obstipation	0%	27%	0%	3%	3%	2%	3%	3%	1%
Nausea	9%	33%	11%	16%	3%	3%	18%	6%	3%
Diarrhö	18%	9%	2%	14%	10%	1%	16%	5%	0%
Fieber	13%	9%	0%	22%	20%	0%	18%	16%	0%
Tumorblutung		0%			7%			7%	

In allen drei Behandlungsarmen wurde die Therapie gut vertragen. Angegeben ist die prozentuale Häufigkeit der jeweiligen Nebenwirkungen bezogen auf die Gesamtanzahl der Anwendungen.

Chemotherapie-Regimen oder Radiochemotherapie konnten ebenfalls randomisiert werden. In allen drei Behandlungsarmen waren bei mehr als 60 Prozent der Patienten bereits Metastasen vorhanden.

Verträglichkeit der Therapie und Lebensqualität

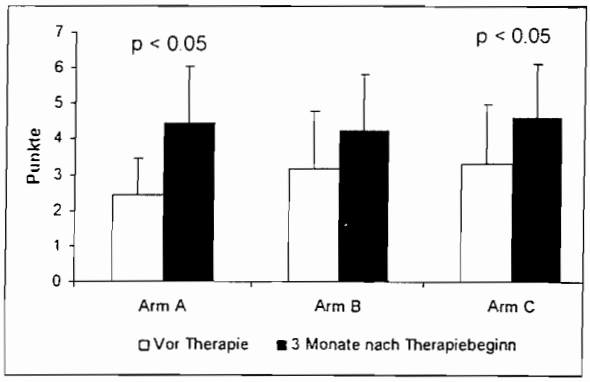
In allen drei Behandlungsarmen war das Nebenwirkungsspektrum moderat und die Therapie wurde gut vertragen. In einem kleinen Prozentsatz zeigten sich jedoch in allen drei Behandlungsarmen auch Nebenwirkungen nach WHO-Grad III, die behandlungsbedürftig waren (*Tabelle 2*). Das Nebenwirkungsspektrum lag unter Gemcitabine-Monotherapie im Rahmen der Nebenwirkungen, die auch in anderen publizierten Studien auftraten. Unter Ukrain-Monotherapie wurden vor allem hämatologische Nebenwirkungen (meist leicht- bis mittelgradige Thrombozytopenien, selten Leukopenien), gastrointestinalen Nebenwirkungen (Nausea, Obstipation und Diarrhö), leichter Blutdruckabfall nach Applikation und leichte Temperaturerhöhung beobachtet. Interessanterweise war unter der Kombinationstherapie keine Addition der Nebenwirkungen zu beobachten. Der Anteil an behandlungsbedürftigen Nebenwirkungen lag vielmehr im Bereich der Monotherapie-Behandlungsarme. Deutlich hervorzuheben ist jedoch, dass sich bei jeweils 7 Prozent (2 Patienten) in beiden Behandlungsarmen, in denen Ukrain verwendet wurde, Tumorblutungen zeigten, die interventionell gestillt werden mussten. In jedem der drei Therapiearme haben sich weiter jeweils 2 Patienten entschieden, die Therapie nicht zu beenden, und sind vorzeitig aus der Studie ausgeschieden.

Da der Erhalt der Lebensqualität in der palliativen Tumortherapie des fortgeschrittenen Pankreaskarzinoms ein primäres Therapieziel darstellt, wurde im Rahmen der Studie zu jedem Therapiezyklus die Selbsteinschätzung der Lebensqualität nach dem Evaluationsbogen der European Organisation for Research and Treatment of Cancer (EORTC-QLQ-C30) erfasst. Wie bereits in früheren Studien dokumentiert, zeigte sich ein signifikanter Anstieg der Lebensqualität der Patienten 3 Monate nach Beginn der Therapie mit Gemcitabine (*Abbildung 1*). Doch auch unter Monotherapie mit Ukrain (statistisch nicht signifikant) und unter Kombinationstherapie (statistisch signifikant) zeigte sich ein deutlicher Anstieg der Lebensqualität 3 Monate nach Therapiebeginn.

Ansprechen der Therapie und Überlebenszeiten

Zur Therapiekontrolle wurden alle 3 Monate Röntgenaufnahmen des Thorax, kontrastmittelverstärkte Computertomographien der Oberbauchorgane und Ultraschalluntersuchungen des Abdomens durchgeführt. Tumormarker wurden bei jedem Therapiezyklus bestimmt.

Die Tumormarkerbestimmungen zeigten keinen statistisch signifikanten Unterschied zwischen den drei Behandlungsarmen im Verlauf der Therapie (*Tabelle 3*). Die Grössenbestimmung des Primärtumors sowie vorhandener Metastasen wurde im kontrastmittelverstärkten Computertomogramm vorgenommen. Dabei zeigte sich nach 3 Monaten unter Thera-



Selbsteinschätzung der Lebensqualität 3 Monate nach Therapiebeginn. (Frage 29 des EORTC-QLQ-C30-Erhebungsbogens)

Ukrain beim fortgeschrittenen Pankreaskarzinom

Tabelle 3: **Ansprechen der Therapie**

	Arm A Gemcitabine	Arm B Ukrain	Arm C Ukrain/Gemcitabine
Tumormarker (CA19-9)			
Complete Response (CR)	1/15	0/15	1/20
Partial Response (PR)	5/15	4/15	7/20
No Change (NC)	5/15	5/15	9/20
Progressive Disease (PD)	4/15	5/15	3/20
Computertomographie nach 3 Monaten			
Complete Response (CR)	0/28	0/20	0/28
Partial Response (PR)	1/28	2/20	6/28
No Change (NC)	8/28	13/20	17/28
Progressive Disease (PD)	19/28	5/20	5/28
CR+PR+NC vs. PD	9/19	15/5**	23/5***
Überlebensraten			
Nach 6 Monaten	26%	65%*	74%**
Nach 9 Monaten	13%	40%	56%**
Nach 12 Monaten	13%	29%	32%
Mediane Überlebenszeit in Monaten	5,2	7,9**	10,4**

*: $p < 0,05$ im Vergleich zur Gemcitabine-Monotherapie (Arm A)
**: $p < 0,01$ im Vergleich zur Gemcitabine-Monotherapie (Arm A)
***: $p < 0,001$ im Vergleich zur Gemcitabine-Monotherapie (Arm A)

Ansprechraten (Tumormarker und kontrastmittelverstärkte Computertomographie), sowie Überlebensdaten in den drei Behandlungsarmen.

pie mit Gemcitabine bei 1 von 28 Patienten eine Teilremission, bei 8 von 28 Patienten zeigte sich keine Veränderung und bei 19 der 28 Patienten fand sich eine Progression. Unter Ukrain-Monotherapie fand sich zum gleichen Zeitpunkt bei 2 der bis zum Auswertungszeitpunkt erhobenen 20 Patienten eine Teilremission, bei 13 der 20 Patienten zeigte die Computertomographie einen unveränderten Zustand und bei nur 5 der 20 Patienten waren der Tumor oder die Metastasen grössenprogredient. In der Kombinationstherapie zeigte sich bei 6 der 28 Patienten eine Teilremission, bei weiteren 17 von 28 war der Befund unverändert und nur bei 5 von 28 war der Befund grössenprogredient.

Im Vergleich der Anzahl von Patienten mit einer Progression der Erkrankung und den Patienten mit einer stabilen Tumorlast oder Grössenreduktion des Befundes zeigte sich ein signifikanter Unterschied der Behandlungsarme B (Ukrain-Monotherapie) und C (Kombinationstherapie) gegenüber der Monotherapie mit Gemcitabine (Arm A). Im Bezug auf die Überlebensraten nach 6,9 und 12 Monaten zeigte sich ein signifikanter Unterschied der Behandlungsarme B und C im Vergleich zum Therapiearm A: Während nach 6 Monaten unter Gemcitabine-Monotherapie nur noch 26 Prozent der Patienten lebten, waren in den beiden anderen Therapiearmen noch 65 (Arm B) beziehungsweise 74 Prozent (Arm C) der Patienten am Leben. Nach 9 Monaten lebten unter der Kombinationstherapie noch signifikant mehr Patienten als in den beiden anderen Therapiearmen. Nach 12 Monaten zeigte sich kein statistisch signifikanter Unterschied mehr zwischen den verschiedenen Behandlungsarmen. Die mediane Überlebenszeit betrug unter Gemcitabine-Monotherapie 5,2 Monate, unter Ukrainmonotherapie 7,9 Monate, und Patienten, die die Kombinationstherapie erhielten, lebten im Median 10,4 Monate.

Fazit: Eine weitere Evaluation von Ukrain ist erforderlich

Da das Pankreaskarzinom durch eine sehr schlechte Prognose gekennzeichnet ist und leider nur ein kleiner Teil der Patienten überhaupt einer chirurgischen Resektion und somit einer potenziell kurativen Therapie zugeführt werden kann, ist der Bedarf nach einer gut verträglichen palliativen Therapie mit dem Ziel der Linderung tumorbedingter Beschwerden, Erhaltung der Lebensqualität und Verbesserung der Prognose gegeben. Mit Gemcitabine steht heute ein Medikament zu Verfügung, das zumindest teilweise diese Ansprüche erfüllt. Die Ulmer Studie bestätigt andere Untersuchungen, nach denen sich die Lebensqualität der Patienten unter Therapie mit Gemcitabine verbessert. Ebenfalls hat die Therapie einen, wenn auch marginalen, Einfluss auf die Überlebensprognose. Das in dieser Studie ermittelte mediane Überleben deckt sich mit den Studienergebnissen anderer Gruppen. Ukrain wurde seit mehr als 20 Jahren vor allem in osteuropäischen Kliniken eingesetzt. In der Literatur findet sich weiter eine grosse Anzahl an Einzelfallbeschreibungen, in denen teilweise erstaunliche Behandlungsergebnisse beschrieben werden. Dennoch ist das Präparat aufgrund der unbefriedigenden Datenlage und der teils widersprüchlichen Erhebungen zum Wirkungsmechanismus des Präparates umstritten. Mit der vorgelegten universitären Studie zur Behandlung des fortgeschrittenen Pankreaskarzinoms wurde ein wichtiger Grundstein zur wissenschaftlichen Evaluierung des Präparates gelegt. Ukrain zeigte in der monozentrischen Studie beim Pankreaskarzinom, als Monotherapeutikum sowie – ausgeprägter – in

Ukrain beim fortgeschrittenen Pankreaskarzinom

Kombination mit Gemcitabine, einen deutlichen Effekt auf den Verlauf der Erkrankung im untersuchten Patientenkollektiv. Die Autoren halten deshalb eine weitere wissenschaftliche Evaluierung der Substanz für gerechtfertigt. Die vorgestellte klinische Studie wurde publiziert in: Langenbecks Archives of Surgery, Volume 386, Ausgabe 8, 2002 (13).

1. Beger H.G., Buchler M.W., Friess H.: Surgical results and indications for adjuvant measures in pancreatic cancer. Chirurg 1994; 65: 246–252.

2. Beger H.G., Gansauge F., Buchler M.W., Link K.H.: Intraaterial adjuvant chemotherapy after pancreaticoduodenectomy for pancreatic cancer. World J Surg. 1999; 23; 946–949.

3. Gall F.P., Kessler H.: [Early cancer of the exocrine pancreas: diagnosis and prognosis]. Chirurg 1987; 58: 78–83.

4. Warshaw A.L.: Implications of peritoneal cytology for staging of early pancreatic cancer. Am J Surg. 1991; 161: 26–29.

5. Gudjonsson B.: Cancer of the pancreas. 50 years of surgery. Cancer 1987; 60: 2284–2303.

6. Gudjonsson B.: Survival statistics gone awry: pancreatic cancer, a case in point. J Clin Gastroenterol. 2002; 35: 180–184.

7. Nitecki S.S., Sarr M.G., Colby T.V., van Heerden J.A.: Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg. 1995; 221: 59–66.

8. Burris H.A., III, Moore M.J., Andersen J, Green M.R., Rothenberg M.L., Modiano M.R. et al.: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15: 2403–2413.

9. Kornek G.V., Potter R., Selzer E., Schratter A., Ulrich-Pur H., Rogy M. et al.: Combined radiochemotherapy of locally advanced unresectable pancreatic adenocarcinoma with mitomycin C plus 24-hour continuous infusional gemcitabine. Int J Radiat Oncol Biol Phys. 2001; 49: 665–671.

10. Kurtz J.E., Kohser F., Negrier S., Trillet-Lenoir V., Walter S., Limacher J.M. et al.: Gemcitabine and protracted 5-FU for advanced pancreatic cancer. A phase II study. Hepatogastroenterology 2000; 47: 1450–1453.

11. Oettle H., Arning M., Pelzer U., Arnold D., Stroszczynski C., Langrehr J. et al.: A phase II trial of gemcitabine in combination with 5-fluorouracil (24-hour) and folinic acid in patients with chemonaive advanced pancreatic cancer. Ann Oncol. 2000; 11: 1267–1272.

12. Ramadani, M., Gansauge, S., Braumüller, H., Schlosser, S., Beger, H. G., und Gansauge, F.: Selektive Apoptoseinduktion in Pankreaskarzinomzellinien durch NSC-631570. Langenbecks Arch Surg. Suppl. I (Forumband 2000): 79–83.

13. Gansauge F., Ramadani M., Pressmar J., Gansauge S., Muehling B., Stecker K. et al.: NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial. Langenbecks Arch Surg. 2002; 386: 570–574. ●

Prof. em. Dr. med. Hans G. Beger
Forschungsgruppe Pankreaskarzinom
Universität Ulm
Steinhövelstr.9,
D-89075 Ulm
Tel. 0049 731-500 267 80
Fax 0049 731-500 267 86
E-Mail: hans.beger@medizin.uni-ulm.de

Interessenlage: Die Phase-II-Studie wurde mit Forschungsmitteln der Universität Ulm finanziert. Die Studienmedikation wurde teilweise vom Hersteller zur Verfügung gestellt. Es fand ein neutrales externes Studienmonitoring statt, die statistische Auswertung führte die Abteilung Biometrie der Universität Ulm durch.

Zentrum für onkologische, endokrinologische und minimalinvasive Chirurgie

Prof. em. Dr. med.
Hans G. Beger
PD Dr. med.
Frank Gansauge
PD Dr. med.
Bertram Poch
PD Dr. med.
Michael Schwarz

Abschlussauswertung Ukrain Studie

Priv. Doz. Dr. med. Frank Gansauge

Zentrum für onkologische, endokrinologische und minimalinvasive Chirurgie
Silcherstr. 36, 89231 Neu-Ulm

Die Studie begann im Oktober 1999. Im Juni 2001 wurde die Studie geschlossen, in jeden der drei Studienarme wurden 30 Patienten rekrutiert.
Arm A (Gemcitabine)
Arm B (Ukrain®)
Arm C (Gemcitabine + Ukrain®)

In jedem Studienarm waren jeweils 2 Therapieabbrecher zu beobachten, diese Patienten wurden in die Endauswertung im März 2003 nicht mehr miteinbezogen.

Bezüglich der Patientendaten siehe Publikation (Gansage et al., Langenbeck`s Archieves of Surgery (2002) 386: 570-574).

Im Studienarm A (Gemcitabine Monotherapie) sind mittlerweile alle Patienten verstorben, im Arm B (Ukrain® Monotherapie) sind 2 Patienten (7,1%) 26 bzw. 28 Monate nach Therapiebeginn am Leben, Im Arm C (Gemcitabine + Ukrain®) sind alle Patienten mittlerweile verstorben.

Bezüglich des Nebenwirkungsprofils und der Lebensqualität siehe Publikation (Gansage et al., Langenbeck`s Archieves of Surgery (2002) 386: 570-574).

Illertalklinik
Abt. Viszeralchirurgie
Krankenhausstraße 7
89257 Illertissen
Tel. FAX +49 (0) 7303 177 188
clinic-eurosurgery.de

Praxis
Silcherstraße 36
89231 Neu-Ulm
Tel. +49 (0) 731 - 715 76 0
FAX +49 (0) 731 - 715 76 350
uniz-eurosurgery.de

In der Endauswertung zeigt sich folgendes Ergebnis:

Mediane Überlebenszeit (Kaplan-Meier-Lifetime analysis)

Arm A (Gemcitabine Monotherapie)	4,8	Monate
Arm B (Ukrain® Monotherapie)	8,1	Monate
Arm C (Gemcitabine + Ukrain®)	9,3	Monate

Hieraus ergeben sich folgende Signifikanzen (Chi-Quadrat-Test)

Arm A versus Arm B:	$p < 0,01$
Arm A versus Arm C:	$p < 0,02$
Arm B versus Arm C:	nicht signifikant ($p=0,67$)

Überlebensraten

	6 Monate	9 Monate	12 Monate	24 Monate
Arm A	32%	11%	11%	0%
Arm B	**61%***	**43%****	32%	18%
Arm C	**64%***	**54%****	29%	4%

Zusammenfassung

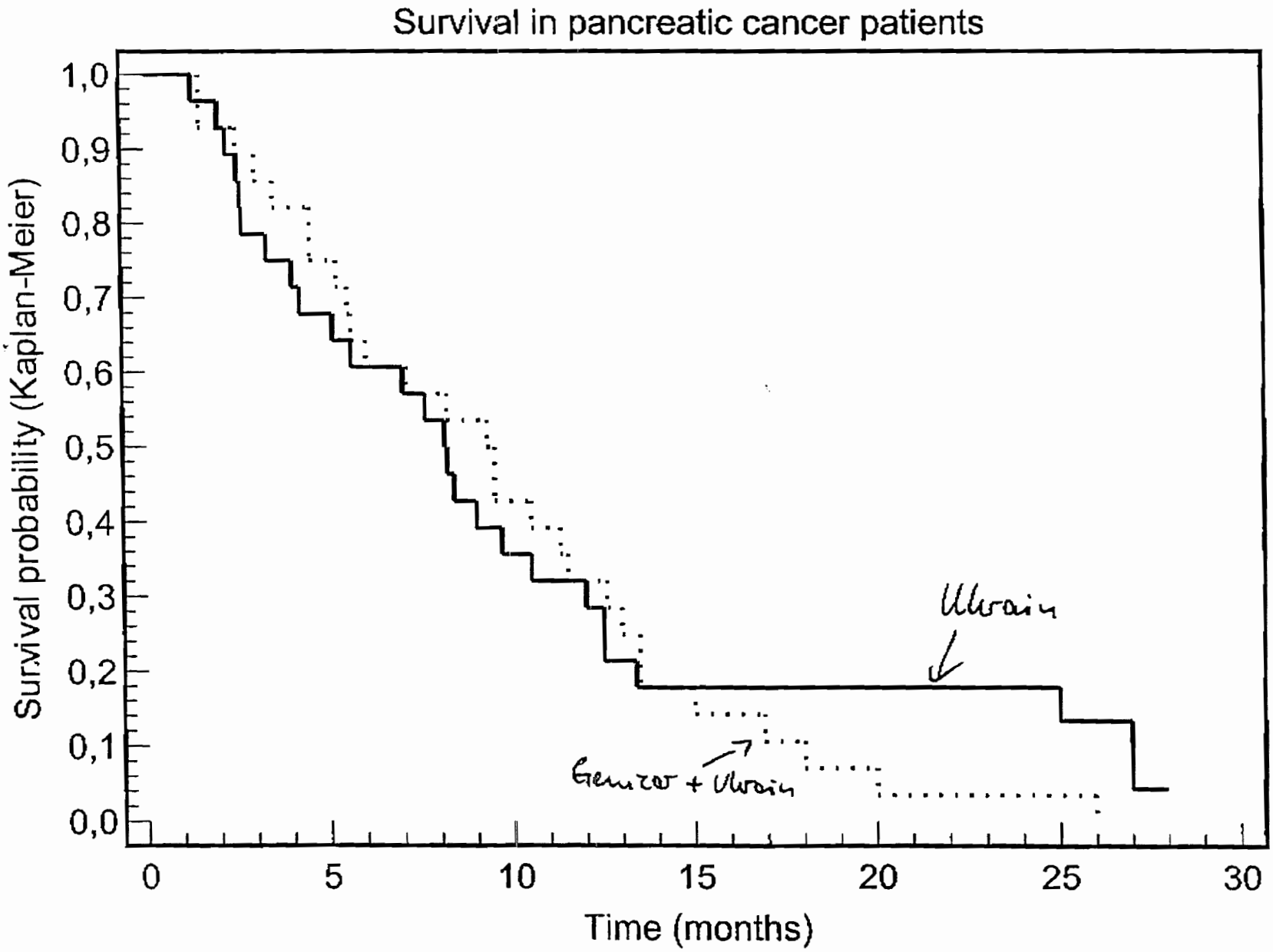
In der Endauswertung der Studie "Ukrain in der palliativen Behandlung des fortgeschrittenen Pankreaskarzinoms" wurden die Ergebnisse der Zwischenauswertung bestätigt. Während

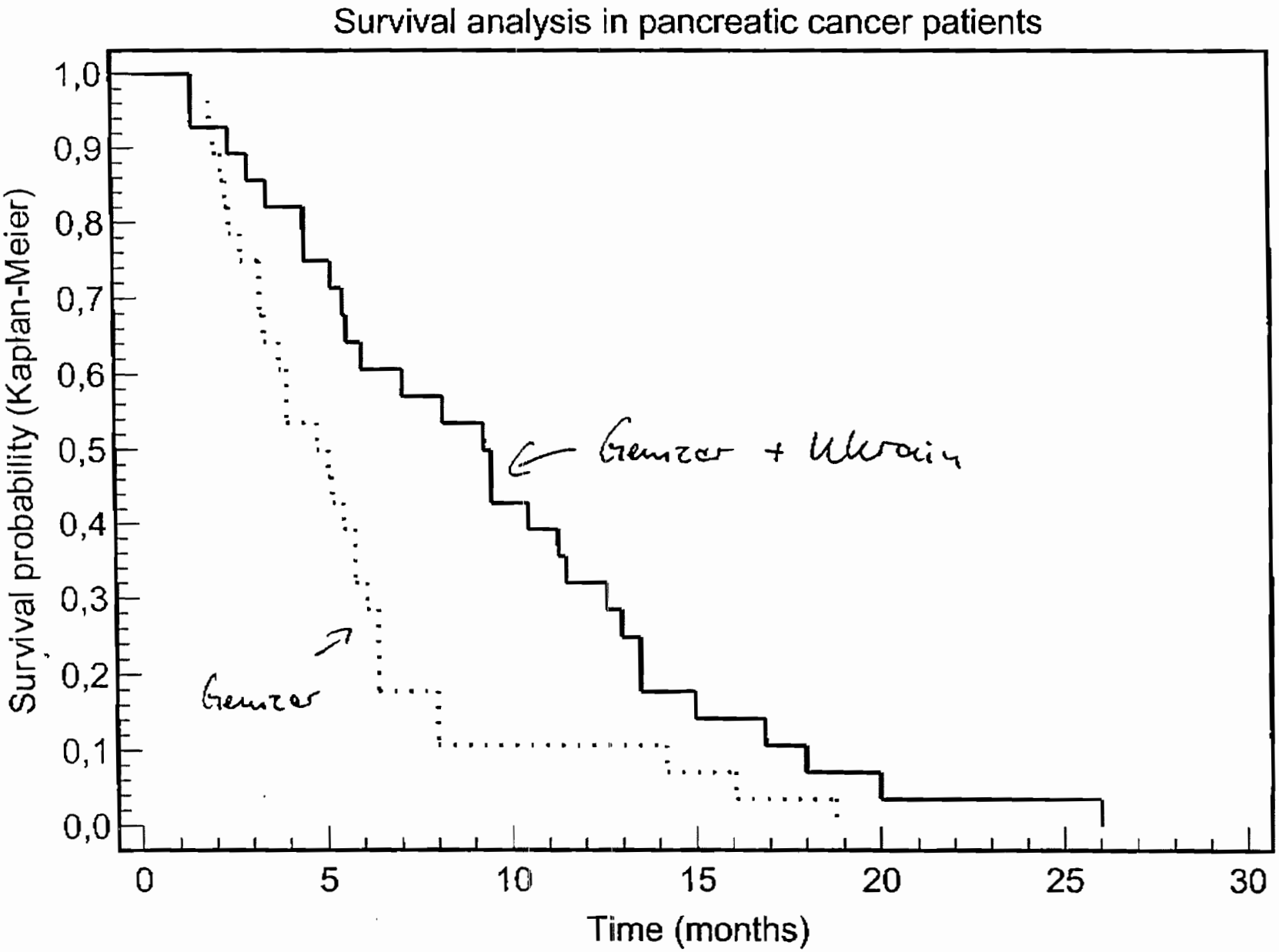
sich die mediane Überlebenszeit im Arm C etwas verschlechterte, blieben die medianen Überlebenszeiten im Arm A und B nahezu konstant.

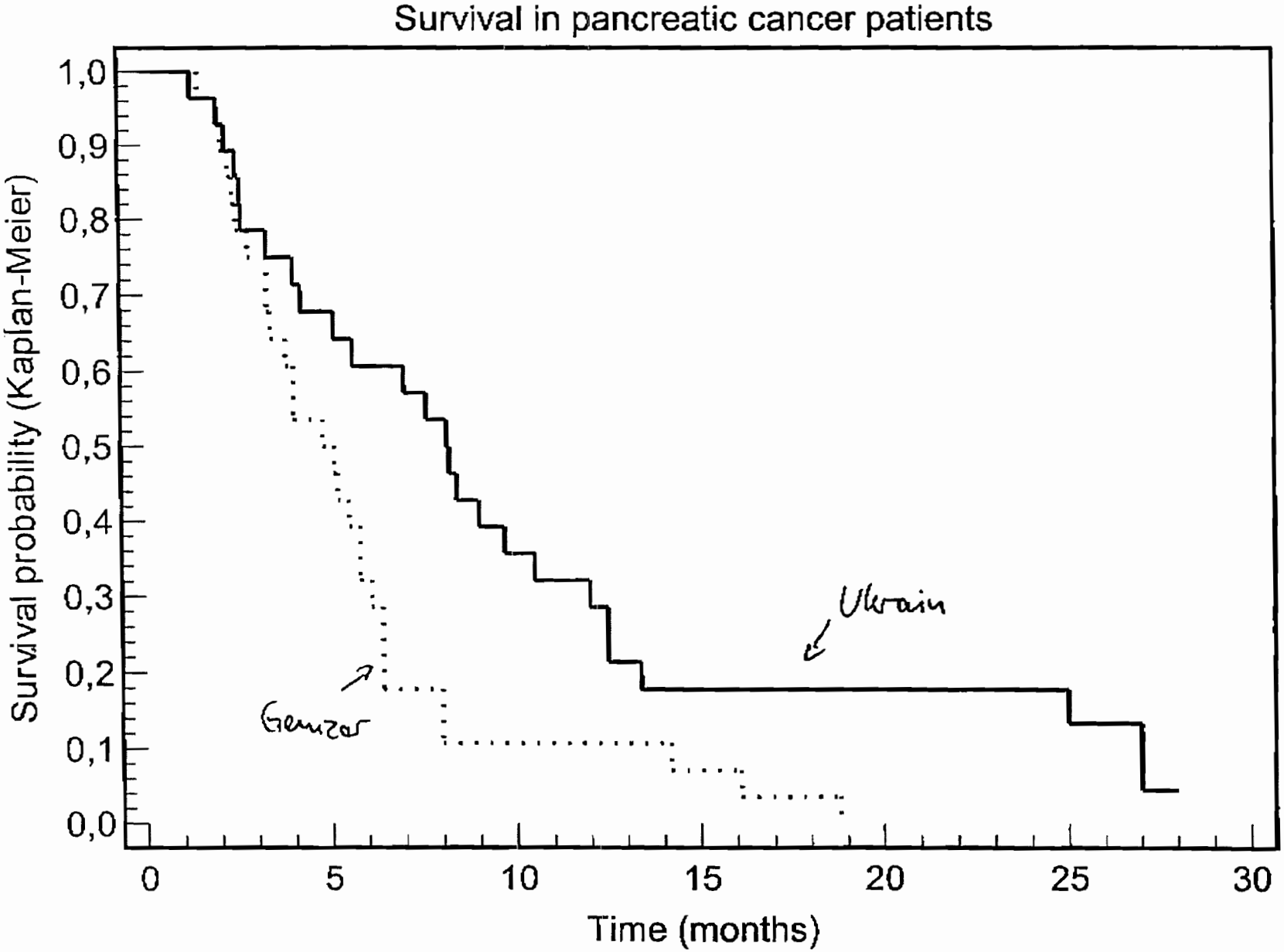
In der Schlussfolgerung der Studie zeigt sich, dass Ukrain® gut vertragen wird und auch im ambulanten Bereich problemlos angewendet werden kann. Im Vergleich zur Gemcitabinetherapie kommt es zu einer signifikanten Verlängerung der Überlebenszeit. Die Kombinationstherapie Gemcitabine + Ukrain® zeigt keinen Vorteil zur Ukrain®-Monotherapie. Aus diesem Grunde empfehlen wir auf Grund unserer Studienergebnisse in der palliativen Behandlung des fortgeschrittenen Pankreaskarzinoms die Ukrain®-Monotherapie.

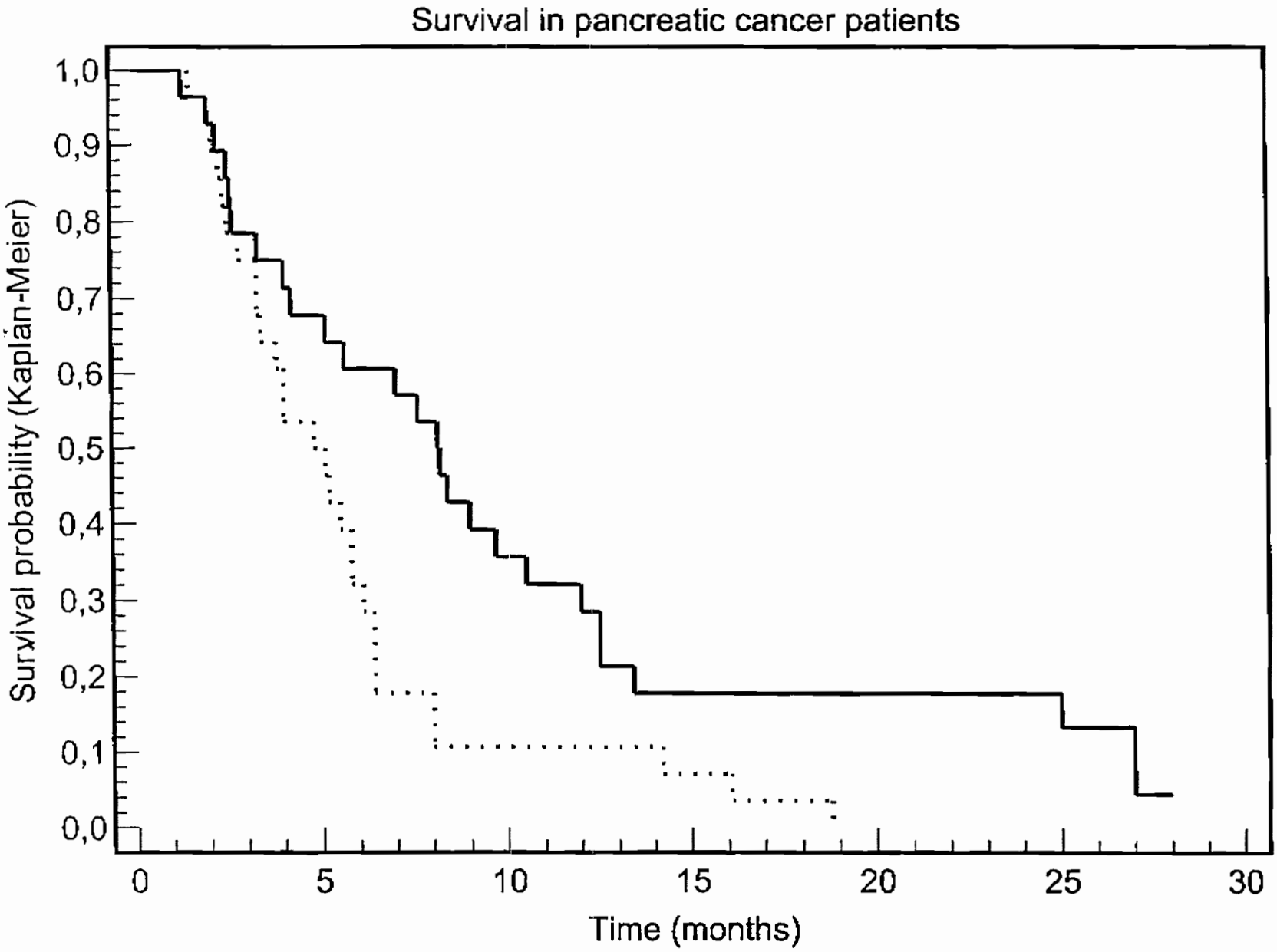
Neu-Ulm, den 13.03.2003

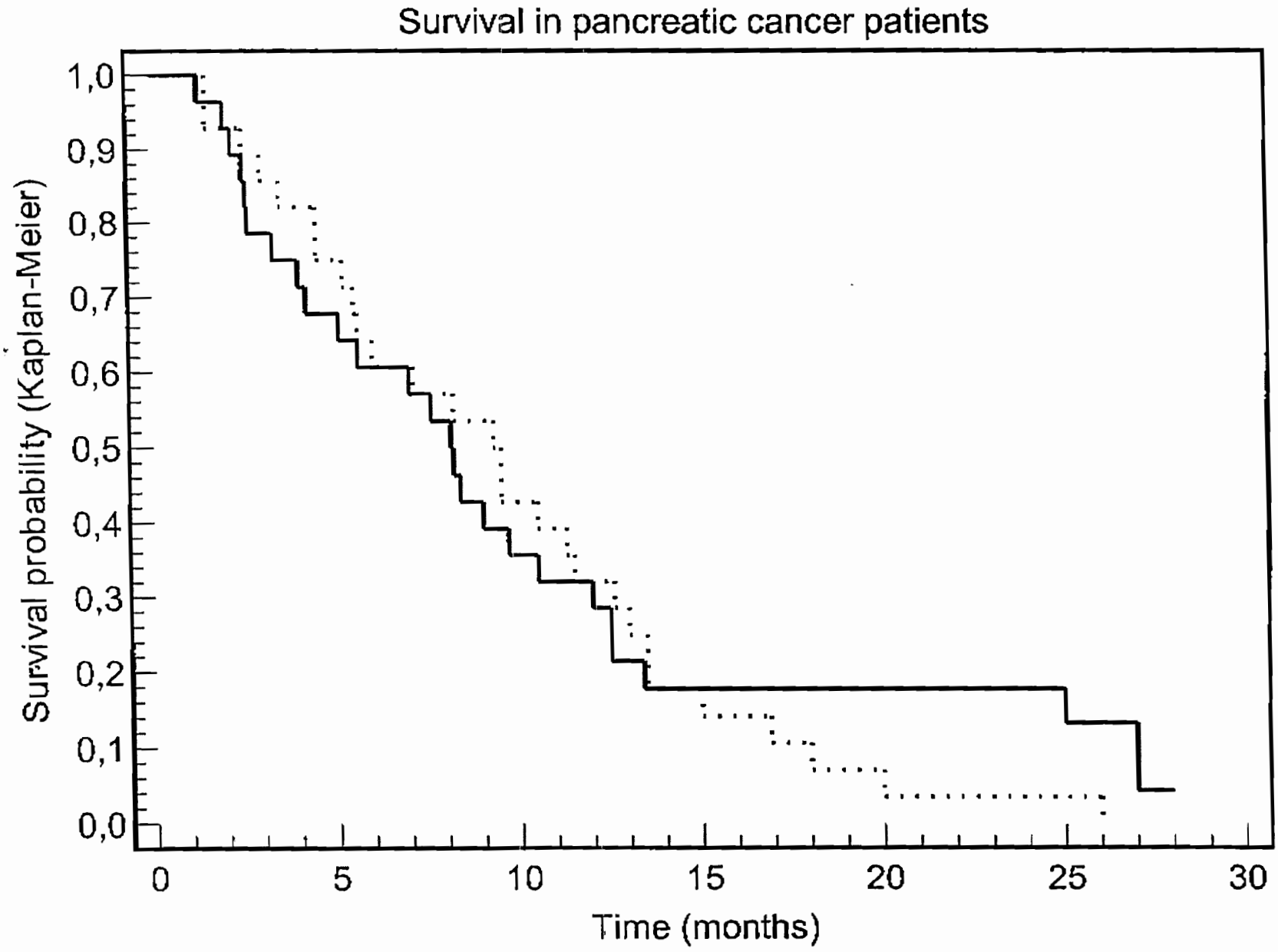
Priv. Doz. Dr. med. Frank Gansauge


Survival in pancreatic cancer patients
Survival probability (Kaplan-Meier)
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
5
10
15
20
25
30
Time (months)
Ulvain
Gemzar + Ulvain




Survival in pancreatic cancer patients
Survival probability (Kaplan-Meier)
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
5
10
15
20
25
30
Time (months)
Ukrain
Genzar


Survival in pancreatic cancer patients
Survival probability (Kaplán-Meier)
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
5
10
15
20
25
30
Time (months)


Survival in pancreatic cancer patients
Survival probability (Kaplan-Meier)
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
5
10
15
20
25
30
Time (months)

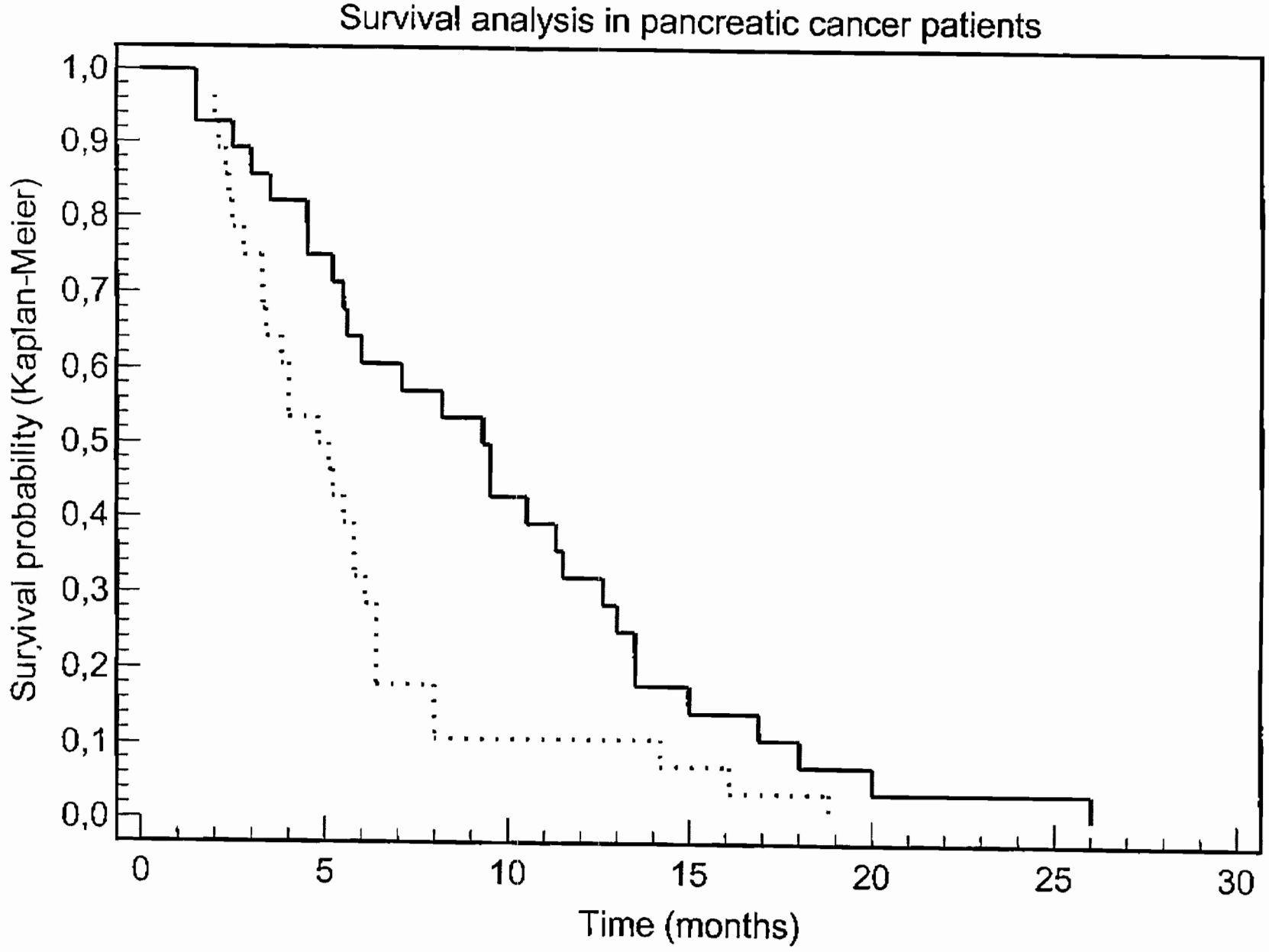

Survival analysis in pancreatic cancer patients
Survival probability (Kaplan-Meier)
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
5
10
15
20
25
30
Time (months)

図09