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

ORIGINAL ARTICLE

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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

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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/m^2 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/m^2 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).

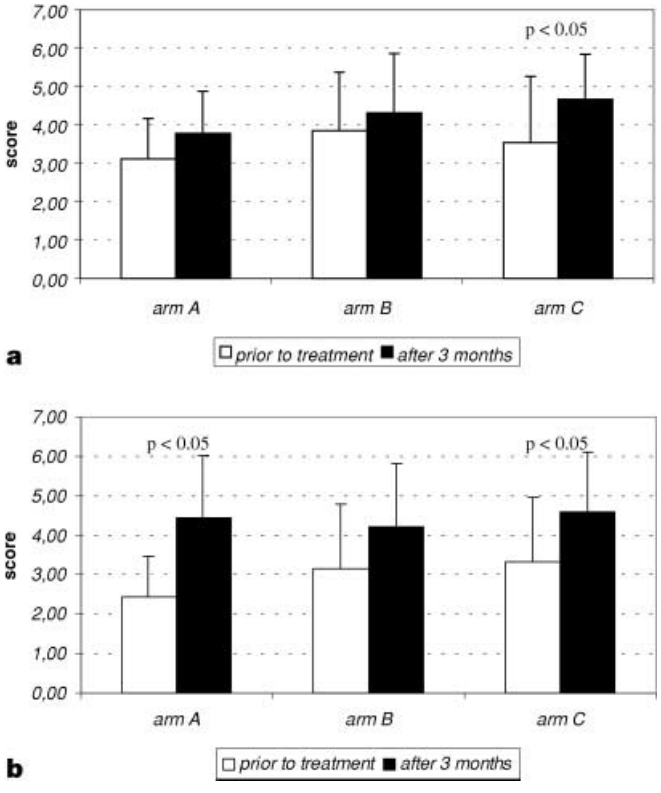

Fig. 1 Self-estimation of the health status (**a)** and the quality of life status (**b)** in palliatively treated pancreatic cancer patients prior to treatment and after 3 months of therapy. **a** With regard to the self-estimation of the health status a significant difference was observed in arm C,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

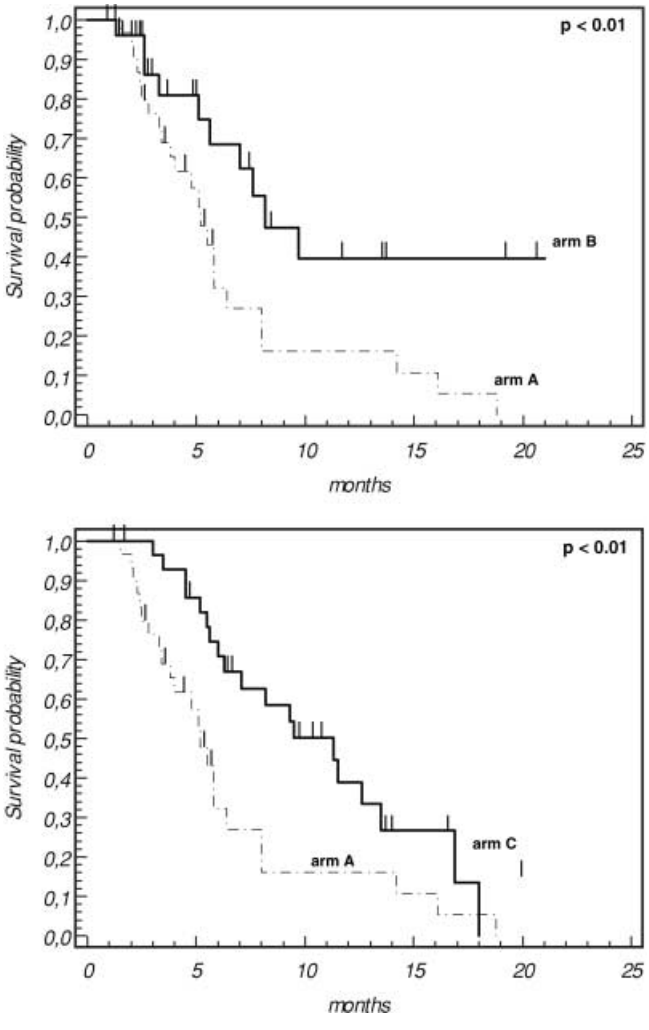

Fig. 2a,b Kaplan-Meier survival curves of advanced pancreatic cancer patients palliatively treated according to arm A, arm B, or arm C. **a** Patients who received NSC-631570 monotherapy (arm A, *solid line*) lived significantly longer as compared to patients treated with gemcitabine monotherapy (arm 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