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Efficacy of Ukrain in the treatment of pancreatic cancer

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Abstract *Background:* This monocentric study evaluated the effect of Ukrain in the treatment of pancreatic cancer. *Material and methods:* Between January 1996 and December 1999 we treated 21 patients with 10 mg Ukrain every second day ×10. The control group received supportive treatment only. *Results:* Ukrain treatment was well tolerated. Mean values on pain measure and Karnofsky index were significantly better in the Ukrain group than in controls ($P<0.05$). One-year survival was 76% in the Ukrain group, compared to 9.5% in the control group. Median survival after treatment with Ukrain was 574 days, compared to 197 days in the control group. *Conclusions:* Our data demonstrate that Ukrain improves quality of life in patients suffering from advanced pancreatic cancer and significantly prolongs survival time in these patients.

Keywords Pancreatic cancer · Ukrain (NSC-631570) · Palliative surgery

Introduction

Pancreatic cancer accounts for 2–3% of malignant tumors and is the sixth most common oncological disease and the fifth most common cause of cancer death, with an incidence of approx. 9 per 100,000 [1, 2]. It is a malignancy that causes late symptoms, and diagnosis is therefore late and cure rare. At the time of diagnosis most patients show progression of the disease beyond the pancreas, either through the direct invasion of neighboring structures or metastases in regional lymph nodes, liver, peritoneum, lungs, bones, or brain. Median survival time is approx. 4–6 months after diagnosis. Fewer than 10% of patients survive 1 year after diagnosis, and many suffer from increasingly severe pain, nausea and vomiting, anorexia, weight loss, and weakness as the disease progresses. Five-year survival in cases of early diagnosis is 3.6% [3]. In the few cases in which early diagnosis is made, surgical pancreatico-duodenectomy may be attempted by those with skill and experience in performing this challenging operation. However, although operative mortality rates have much improved, surgery has only a slight effect on survival time. Adjuvant chemoradiation therapy has shown prolonged survival time in some trials but not in others [4].

Recent studies of chemotherapy for advanced pancreatic cancer have used gemcitabine, a novel nucleoside analogue. A phase II trial by Casper et al. [5] observed a partial response of 11%. A phase III study by Burris et al. [6] compared the effectiveness of gemcitabine and 5-fluorouracil (5-FU, NSC-19893) in patients with newly diagnosed advanced pancreatic carcinoma. Clinical benefit was measured by a combination of visual analogue scale, change in analgesic use, and improvement in

Karnofsky Performance Status. Clinical benefit response was experienced by 23.8% of gemcitabine-treated patients, compared to 4.8% of 5-FU treated patients.

Because of the harmful effects of chemotherapy on healthy cells, many physicians carefully consider its use in the case of pancreatic cancer. The rationale of its use is often more to slow the spread of metastases and to improve the quality of life than to inhibit growth of the main tumor. The effect of chemotherapy on survival in pancreatic cancer is negligible. Gemcitabine is now used as standard therapy for advanced pancreatic cancer, but unfortunately it prolongs median survival of patients by only 4–6 weeks. The study by Burris et al. [6] found the median survival time to be only 5.65 and 4.41 months in patients treated with gemcitabine and 5-FU, respectively; the 12-month survival rate was 18% in gemcitabine patients and 2% in 5-FU patients. Unfortunately, all patients had progressed within 14 months of starting therapy, and no patient survived beyond 19 months.

Ukrain (NSC-631570; Nowicky Pharma, Vienna, Austria) is a semisynthetic compound from alkaloids from *Chelidonium majus* L. and thiophosphoric acid triaziridide that is known to be an immune modulator [7]. It has demonstrated considerable promise in the treatment of a variety of oncological diseases [8, 9, 10, 11, 12]. It accumulates in cancer cells within minutes of administration, a property that can be seen due to its autofluorescence under UV light [13]. Although the exact mode of action of Ukrain is not yet known, it is destructive to cancer cells while leaving normal cells undamaged [14]. Ukrain develops its anticancer activity via a dose-related inhibition of DNA, RNA, and protein synthesis [12, 13]. This inhibition is limited to malignant cells [14, 15, 16]. The selective inhibition reflects the preferential uptake of Ukrain by tumor cells, as can be measured by monitoring the fluorescence of Ukrain within cells [16].

In vitro tests at the National Cancer Institute have shown Ukrain to be effective and malignocytolytic against all human cancer cell lines tested whereas 5-FU did not reduce tumor cell mass but only inhibited the growth of malignant cell lines [15]. Ukrain has been shown to induce apoptosis (programmed cell death) in malignant cells [16]. We previously conducted a study comparing Ukrain with 5-FU in colorectal cancer. The results in the Ukrain-treated group were much better than those in the 5-FU group, and the in vitro effectiveness of Ukrain in the cancer lines screening panel was much higher than that with 5-FU. Moreover, during 1995 we treated three pancreatic cancer patients with Ukrain at their own insistence, with surprisingly encouraging results. Standard treatment at our clinic at that time was chemotherapy combining 5-FU, doxorubicin, and mitomycin C, which had only a negligible effect on survival in pancreatic cancer patients. In the later study by Burris et al. [6] median survival of 5-FU treated patients was only 4.41 months. Other studies have not demonstrated any advantage of combined chemotherapy regimens compared to 5-FU alone [17, 18, 19]. Many possible severe side effects of 5-FU therapy such as myelosuppression, ulceration of the gastrointestinal tract, cardiac ischemic episodes, and renal failure must be taken into consideration in patients already suffering from a severe disease.

Because of the unsatisfactory results of standard therapy and the encouraging results of Ukrain treatment we initiated this pilot study to investigate whether Ukrain would be effective in controlling the growth of pancreatic cancer and improving the quality of life for patients in late stages of this disease where prognosis is extremely poor.

Patients and methods

Patients

This controlled pilot study included 42 patients with pathologically diagnosed pancreatic cancer at the Department of General Surgery, National Medical University Kyiv, Ukraine between January 1996 and December 1999. None of the patients had adenocarcinoma of the distal bile duct, ampulla, or duodenum. Most had a tumor in the head of the pancreas, but two patients from the Ukrain group and four from the control group had pancreas body lesions. Most patients had pain at entry into the study. Patient characteristics are presented in Table 1.

After surgery, every patient was offered chemotherapy and was informed about the probable results of chemotherapy, and six patients decided for treatment with chemotherapy. Only patients who refused chemotherapy were proposed to enter the study. Forty patients were not amenable to surgical resection; reasons for unresectability were proximity to mesenteric vessels, adherence to retroperitoneum, positive peripanceatic lymph nodes, advanced age, and concomitant diseases. Two patients underwent pancreaticoduodenectomy. Patients received biliary or gastric bypasses when they had signs of biliary or gastric obstruction. Only two patients from the Ukrain group and three from the control group had no signs of biliary obstruction. Three patients from theUkrain group and four from the control group had gastric obstruction and underwent gastric bypass.

Patient assignment

The Pharmacological Committee from the Ministry of Health of Ukraine gave permission to conduct clinical studies with Ukrain in Ukraine. On the basis of this permission and other documentation the local ethics committee approved the study design. Signed informed consent was obtained from each patient before entry into the study. The 42 patients were randomly assigned to treatment with vitamin C plus Ukrain or vitamin C plus normal saline at the clinic before starting study therapy; eligibility was checked before randomization. Each patient drew a sealed envelope indicating the allocated treatment. Treatment allocation was summarized in a master randomization list. Nurses or physicians filled out the analgesic consumption forms. In addition, performance status was assessed.

Table 1 Characteristics of patients (percentages)

	Ukrain	Control
Age (years)		
Mean	60.7	65.4
Range	40–81	43–83
Sex		
Men	81	47.6
Women	19	52.4
Tumor stage (UICC 1997)		
II	4.8	9.5
III	23.8	23.8
IVA	38.1	42.9
IVB	33.3	23.8
Metastases		
Peritoneal	9.5	14.3
Liver	23.8[a]	14.3
Other	4.8	0
Initial Karnofsky index		
80–90	9.5	33.3
60–70	61.9	61.9
40–50	19	4.8
Initial pain intensity[b]		
6–10	38.1	28.6
4, 5	47.6	57.1
2, 3	14.3	14.3
0, 1	0	0
Initial analgesic consumption[c]		
0–49	9.5	14.3
50–100	57.1	61.9
More than100	33.3	23.8
Pancreatico-duodenectomy	4.8	4.8
Biliary bypass procedure		
Choledocho-duodenostomy	23.8	14.3
Hepatico-jejunostomy	52.4	57.1
Bypass procedure		
Gastric	4.8	4.8
Double	9.5	14.3
Alcoholization of the tumor and biopsy only	4.8	4.8

[a] Some patients had peritoneal and liver metastases
[b] Memorial visual analogue scale
[c] Milligrams of morphine equivalent

Treatment

Ukrain was supplied as a solution ready for injection. Vitamin C was used as solution for injection and as tablets. The Ukrain therapy cycle was defined as 10 mg intravenously, ×10, every other day. A vitamin C cycle was defined as 3 g intravenously, ×10, every other day, and 2.4 g oral divided into three doses on the same days. Patients in the Ukrain group received a Ukrain therapy cycle and a vitamin C therapy cycle on the same days. The control group received a vitamin C cycle and 10 ml intravenously normal saline on the same days. Vitamin C as a solution for injection, 3 g, was diluted in normal saline, 200 ml, and administered as an intravenous infusion over 25 min. Then either 10 mg Ukrain or 10 ml normal saline (control group), was injected in the same vein line over 5 min. High doses of vitamin C were included in the treatment schedule of all study patients because we had earlier observed that high doses of vitamin C improve wound healing and prevent postoperative wound suppuration. Patients did not receive concomitant radiation therapy, chemotherapy, hormonal therapy, or corticosteroids during the study.

Efficacy and safety evaluation

In addition to survival as primary end-point of efficacy, other measures of therapeutic benefit were body weight change, Karnofsky performance status, and pain intensity. Hematological, immunological, and biochemical data were also considered. In some of patients computed tomography data showed response to therapy, but in most of patients ultrasound investigation was used. The principal efficacy end point in this study was overall survival, which was measured from the time of the first day of treatment until death or date of last follow-up. Survival was calculated using the log-rank test. Body weight was measured before and after the study therapy. Karnofsky Performance Status was measured before and after the study therapy. Pain intensity was assessed by analgesic consumption dose and analgesic consumption frequency; change in dose or frequency was taken as equivalent for change in pain intensity. Analgesic consumption was measured on a form filled out by the nurses and physicians (milligrams of morphine equivalent per day). Patients were evaluated by history and physical examinations, complete blood counts, chemistry, immunology profiles, and urinalyses. All signs, symptoms or laboratory abnormalities were assessed by WHO criteria for toxicities.

Results

One-year survival was 76% in the Ukrain group and 9.5% in the control group; 2-year survival was 48% in the Ukrain group and 5% in the control group (Fig. 1). Of 21 patients in the Ukrain group 3 were still alive on 5 January 2002, whereas all patients of the control group had died. Survival for the first patient was 2105 days (more than 5.5 years), for the second patient 1349 days (more than 3.5 years), and for third patient 1363 days (more 3.5 years). Three patients (14.3%) died within 5 months due to progression of the disease, and two died of other diseases (one each of myocardial infarction and heart failure) within 8 months. Six Ukrain patients (28.6%) but no patients from the control group put on weight (7% increase in body weight). Seventeen (81.0%) patients in the Ukrain group showed positive change in analgesic consumption. Median duration of response was 10 months in the Ukrain group. Four patients from the Ukrain group were completely free from pain and did not need analgesics. Two who are still alive do not complain of pain. Both pain and Karnofsky Performance Status improved in ten Ukrain patients. Three Ukrain patients had an improvement in pain and no worsening of Karnofsky Performance Status (Fig. 2). Three Ukrain patients (14.3%) achieved partial tumor response with median duration of 14 months, and nine patients (42.9%)

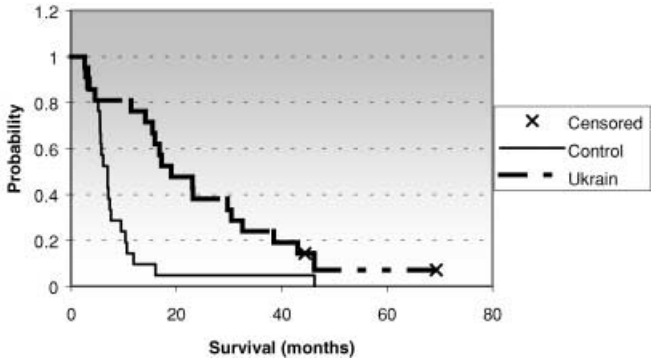

Fig. 1 Kaplan-Meier survival curves in pancreatic cancer patients (n=42)

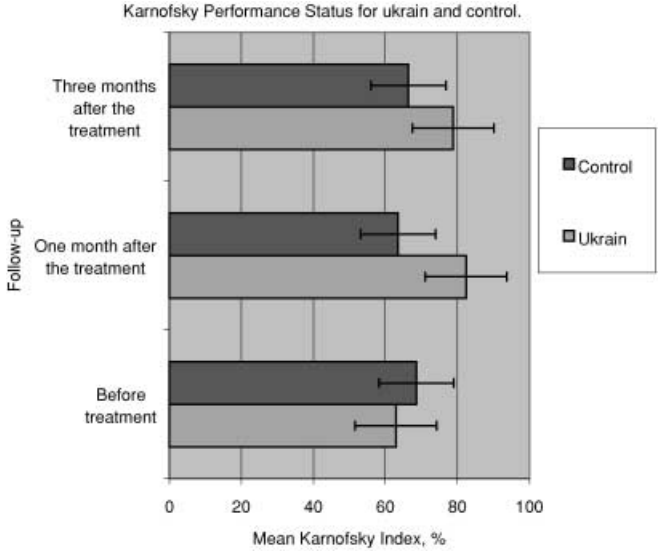

Fig. 2 Karnofsky Performance Status in Ukrain and control groups

had stable disease for 13 months (median value). Three patients (14.3%) from the control group had stable disease with median duration of 5 months; none achieved a complete or partial response.

Blood and urine examinations revealed no negative or toxic effect of Ukrain and moreover showed an improvement in the immune profile in Ukrain-treated patients (Table 2). Both treatment schemes were generally well tolerated. The typical reaction in Ukrain patients was a temperature increase of 1–1.5° which appeared 3–5 h after injection, and which disappeared without use of medication. Temperature increase was observed in those patients who showed partial tumor response (three patients) or stable diseases (seven patients). Usually after the third to fifth injection of Ukrain patients described an improvement in the general condition, with increased appetite and normalization of sleep and decreased local pain.

Table 2 WHO grade toxicity in Ukrain-treated patients (percentages)

	WHO grade				
	0	1	2	3	4
Segmented neutrophils	76.2	23.8	0	0	0
White blood cells	81.0	19.0	0	0	0
Hemoglobin	95.2	4.8	0	0	0
Aspartate transaminase	71.4	23.8	4.8	0	0
Alanine transaminase	66.7	23.8	9.5	0	0
Nausea/vomiting	90.5	4.8	4.8	0	0
Diarrhea	85.7	14.3	0	0	0
Constipation	90.5	9.5	0	0	0
State of consciousness	95.2	4.8	0	0	0
Pain	90.5	9.5	0	0	0
Allergic reactions	100.0	0	0	0	0

Within 2–3 min after the Ukrain injection some patients noted a short-term increase in pain intensity, weakness, itching, and paresthesia in the upper abdomen. These reactions declined without additional treatment. We believe that these reactions were caused by tumor degradation products due to the Ukrain action. However, during treatment with Ukrain we did not observe such symptoms of chemotherapy-related toxicity as neutropenia, anemia, vomiting, or hair loss. There was no allergic reaction in any Ukrain-treated patient.

Discussion

The prognosis in patients with advanced pancreatic cancer is extremely poor. Improving their prognosis requires effective therapy. We designed this controlled pilot study to investigate whether Ukrain prolongs survival or at least lessens disease-related suffering. Gemcitabine was not approved in Ukraine when the study started. The available chemotherapy has shown only a negligible effect on the survival of pancreatic cancer patients, while their quality of life has deteriorated. Therefore it was usual practice to treat advanced pancreatic cancer patients with symptomatic surgery and high doses of vitamin C.

Ukrain revealed a cytotoxic and cytolytic effect on cancer cell lines in vitro. We had conducted a previous study in colorectal cancer comparing Ukrain with 5-FU. The results in the Ukrain-treated group were much better than those in the 5-FU group. In addition, the in vitro effectiveness of Ukrain in the cancer lines screening panel was much higher than that of 5-FU. Moreover, until the start of the pilot study we had treated three pancreatic cancer patients with Ukrain at their own insistence, with encouraging results. These were the reasons for us to conduct a study with Ukrain in pancreatic cancer and for the local ethics committee to approve the study.

Survival in the Ukrain group was surprisingly high (Fig. 2); 12-month survival was 76%, compared to 9.5%

in the control group. We observed a decrease in pain intensity in most Ukrain patients, usually from 10–15 days after the start of treatment. At the start of therapy patients had a short-term (2–3 h) increase in pain intensity in the primary tumor region and at the metastasis sites. In our opinion, these data can be explained by the accumulation of the drug in the tumor tissue and its anticancer effect. Four patients from the Ukrain group became completely free from pain. Two of them who are still alive do not complain of pain.

Gemcitabine is now standard therapy in advanced pancreatic cancer. Our experience with Ukrain in pancreatic cancer includes the treatment of 73 patients until January 2002: 21 in the pilot study, 3 before, and 49 after the study. this experience allows comparison with a gemcitabine-treated control group from the study by Burris at al. [6] Unfortunately, gemcitabine prolongs survival of patients only by 4–6 weeks more than 5-FU. In the study by Burris et al. the median survival duration was only 5.65 and 4.41 months in patients treated with gemcitabine and 5-FU, respectively. The 12-month survival rate was 18% in gemcitabine patients and 2% in 5-FU patients, and there were no survivors beyond 19 months after starting gemcitabine therapy, whereas in our study 12-month survival in the Ukrain group was 76%, and 36-month survival was 23.8%. Gansauge et al. [20] published results of treatment of 90 patients with unresectable pancreatic cancer. 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. Median survival according to Kaplan-Meier analysis was 5.2 months in arm A, 7.9 months in arm B, and 10.4 months in arm C. Actuarial survival rates after 6 months were 26%, 65%, and 74% in arms A, B, and C, respectively.

The optimum schedule for Ukrain therapy in pancreatic cancer with regard to dose and number of therapy cycles has not yet been defined. Further efforts should focus on evaluating Ukrain in patients with an earlier stage of disease and combining it with other treatment modalities, for example, neoadjuvant Ukrain therapy aiming at tumor encapsulation and resectability improvement with subsequent adjuvant therapy. Additional studies are required to evaluate whether more than two Ukrain therapy cycles would further prolong survival in pancreatic cancer patients. Future studies should be conducted with three or four therapy cycles to define an optimum treatment schedule. Our results with Ukrain in the treatment of advanced pancreatic cancer are promising with regard to improving quality of life and lengthening patients' survival. However, these data must be confirmed by further trials.

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References

1. Seeber S, Schütte J (1995) Therapiekonzepte Onkologie. Springer, Berlin Heidelberg New York
2. Fischer DS, Tish Knobf M, Durivage HJ (1997) The cancer chemotherapy handbook. Mosby, St Louis
3. Scnall SF, Macdonalds JS (1996) Chemotherapy of adenocarcinoma of the pancreas. Semin Oncol 23:220–228
4. Alter CL (1996) Palliative and supportive care of patients with pancreas cancer. Semin Oncol 23:229–240
5. Casper ES, Green MR, Kelsen DP, et al (1994) Phase II trial of gemcitabine (2′,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 12:29–34
6. Burris HA, Moore MJ, Andersen J, 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
7. Liepins A, Nowicky JW (1992) Activation of spleen cell lytic activity by the alkaloid thiophosphoric acid derivative: Ukrain. Int J Immunopharmacol 14:8:1437
8. Vatanasapt V, Wongpratoom W, Mairiang P, Mairiang E, Chaiyakam C, Buddhisawasd V, Pairojkul C, Nowicky JW (1991) Preliminary report on clinical experience in the use of Ukrain. Thai Cancer J 17:20
9. Musianowycz J, Judmajer F, Manfreda D, Spängler P, Albrecht H, Hoffmann J, Meijer D (1992) Clinical studies of Ukrain in terminal cancer patients (phase II). Drugs Exp Clin Res 18:45
10. Staniszewski A, Slesak B, Kolodziej J, Harlozinska-Smyrka A, Nowicky JW (1992) Lymphocyte subsets in patients with lung cancer treated with thiophosphoric acid alkaloid derivatives from Chelidonium majus L (Ukrain). Drugs Exp Clin Res 18:63
11. Bondar G, Borota A, Yakovets Y, Zolotukhin S (1998) Comparative evaluation of the complex treatment of rectal cancer patients (chemotherapy and X-ray therapy, Ukrain monotherapy). Drugs Exp Clin Res 24:5–6
12. Uglyanitsa K, Nefyodov L, Nowicky JW, Brzosko W (1998) The effect of Ukrain on cancer of the urinary bladder. 17th International Cancer Congress, Rio de Janeiro, 24–28 August
13. Nowicky JW, Greif M, Hamler F, Hiesmayr W, Staub W (1988) Macroscopic UV-marking through affinity. J Tumor Marker Oncol 33:4
14. Liepins A, Nowicky JW (1991) Ukrain is selectively cytostatic and/or cytotoxic to human tumor and HIV-infected cells but not to normal human cells. In: Recent Advances in Chemotherapy, Anticancer Section, Proceedings of the 17th International Congress of Chemotherapy, Berlin
15. Nowicky JW, Hiesmayr W, Nowicky W, Liepins A (1996) Influence of Ukrain on human xenografts in vitro. Drugs Exp Clin Res 22 [Suppl]

16. Liepins A, Nowicky JW, Bustamante JO, Lam E (1996) Induction of bimodal programmed cell death in malignant cells by the derivative Ukrain (NSC-631570). Drugs Exp Clin Res 22 [Suppl]
17. Kolshelnick Y, Moskvina E, Binder BR, Nowicky JW (1998) Ukrain (NSC-631570) inhibits angiogenic differentiation of human endothelial cells in vitro. Abstracts, 17th International Cancer Congress (Brazil), pp 91–95
18. Sulkowski U, Buchler M, Pederzoli P, Arnold R, Dinse P, Kay A, Haus U, Beger G (1999) A phase II study of high-dose octreotide in patients with unresectable pancreatic carcinoma. Eur J Cancer 35:1805–1808
19. David AK, Vaughn DJ, Holroyde CP, Armstead B, Haller DG (2000) A phase II trial of 5-fluorouracil, leucovorin, and interferon alpha 2A (IFN-alpha 2a) in metastatic pancreatic carcinoma: a Penn Cancer Clinical Trials Group (PCCTG) trial. Am J Clin Oncol 23:37–39
20. Gansauge F, Ramadani M, Pressmar J, Gansauge S, Muehling B, Stecker K, Cammerer G, Leder G, Beger HG (2002) NSC-631570 (Ukrain) in the palliative treatment of pancreatic cancer. Results of a phase II trial. Langenbecks Arch Surg 386:570–574