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-

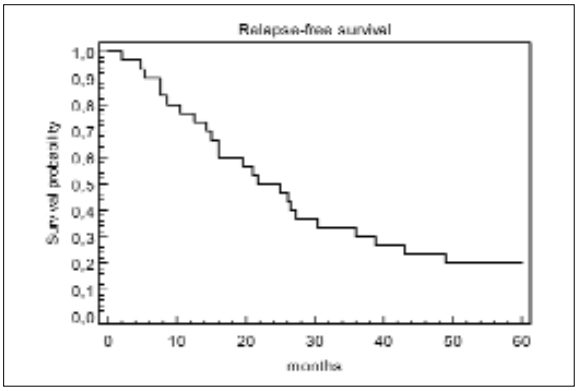


FIGURE 1 The disease-free interval. The disease-free interval following surgery for pancreatic cancer was 21.7 months.

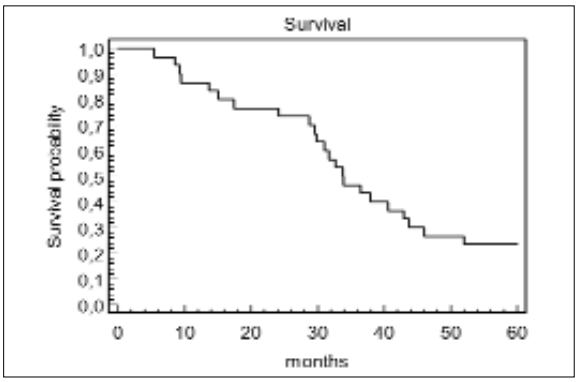


**FIGURE 2** Median survival times according to Kaplan-Meier-regression analysis. The median survival time following surgery for pancreatic cancer was 33.8 months. One patient died 62 months following operation; six patients are still alive without recurrence of the disease.

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