In: R. Klapdor (ed)
Tumor Associated Antigens, Oncogenes, Receptors, Cytokines in Tumor Diagnosis and Therapy at the Beginning of the Nineties.
Cancer of the Breast – State and Trends in Diagnosis and Therapy

Regional Chemotherapy of Advanced Pancreatic Cancer with Mitoxantron-Spherex and Mitomycin-Chemofiltration

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Introduction

The prognosis of pancreatic cancer has not changed during the last decades. Mostly, the diagnosis is made when the tumor has already metastasized or when it has started to infiltrate adjacent structures and – as a results of that – has become inoperable. Other treatment strategies like radiotherapy (9, 17, 18) or different chemotherapy schedules (5, 10, 16, 19) as well as invasive surgery could not improve the prognosis.
A therapeutical attempt with arterial application of the three-drug combination of Mitomycin, Cis-Platin and 5-Fluorouracil via the celiac axis in case of locally non-resectable and metastasized tumors (1) showed satisfying results concerning local tumor response. The median survival time was 10.2 months. This attempt can be optimized regarding the combination of cytotoxics and the appropriate dose. The following study, comparing patients treated with regional therapy and patients treated only symptomatically, is to show whether regional therapy can be a means of life prolongation.

Materials and methods

Patients

A group (I) of 20 patients with advanced non-resectable pancreatic cancer, 9 of them in UICC stage IV with liver metastases, were treated with regional chemotherapy.
A second group (II) of 20 patients who were reluctant to any kind of chemotherapy at the beginning had treatment according to symptoms, such as pain medication, epidural anesthesia and/or parenteral nutrition. 18 patients out of this group had liver metastases. There was no randomiza-

Table I. Intraarterial therapeutic schedule for regional chemotherapy of advanced pancreatic cancer.

Cycle	Day	Therapy			i.a. Infusion time
I	1	10,0 mg	Mitoxantron	Bolus	5 min
		+ 7,5 ml	Spherex		
		+ 5,0 ml	Xylocain		
	2	1000 mg	5-FU		60 min
	3	10,0 mg	Mitoxantron	Bolus	5 min
		+ 7,5 ml	Spherex		
		+ 5,0 ml	Xylocain		
	4	1000 mg	5-FU		60 min
II (4 weeks)	1	30 mg	Mitomycin		30 min
		simultan chemofiltration			60–80 min
	2	1000 mg	5-FU		60 min
	3	1000 mg	5-FU		60 min
III (4 weeks)		diagnostic laparotomy a) primary tumor resection or, in case of non-resectability b) staging biopsies			

tion between group I and II. Performance scale (Karnofsky Index) was comparable in both groups between 30–60%.

Therapy

Group I. Regional chemotherapy consisted of two cycles of intraarterial infusion in four weeks intervals through an angiographically placed celiac axis catheter (table I). In the first course of treatment 10 mg of Mitoxantron each, mixed with 7.5 ml starch microspheres (Spherex, Pharmacia) and 5 ml Xylocain, were given as a bolus infusion on day 1 and 3. On day 2 and 4, 1000 mg of 5-FU were administered as a 60 minutes infusion. The angiographic catheter was kept viable by means of a daily 23 hours continuous perfusion pump infusion of 20.000 i.U. of heparin and was removed at the end of the cycle.
For the second course, after a 4 weeks internal, again a celiac axis catheter was placed in Seldinger technique with its tip in the celiac axis.
30 mg of mitomycin were infused over 30 minutes and systemic drug detoxification by means of chemofiltration was performed simultaneously. Therefore a double lumen filtration catheter (PfM, Cologne, Germany) was inserted in the saphenous vein and the tip proceeded to the inferior vena cava beneath the diaphragm. Filtration was continued over 60–80 minutes until the total amount of filtrate had reached at least 10 liters. Thus immediate and cumulative mitomycin toxicity was lowered (3, 14). On day 2 and 3 each, 1000 mg 5-FU were infused during 60 minutes.
Four to six weeks later a second look surgery was performed, aiming at resection of the primary tumor. In case of nonresectability multiple biopsies were taken at the primary tumor, regional lymph nodes and liver metastases for reasons of staging of the disease and examination of the histological extent of tumor necrosis.[1]

Follow-up parameters

For estimation of therapeutic results the tumor markers CEA and CA 19-9 were taken before the beginning of each cycle. Immediate response to therapy was estimated from markers taken on day 2 and 6. A decrease by at least 50% was considered a PR, a 20–30% reduction was determined a MR. For complete remission a drop into normal ranges was mandatory.
A CT was performed before each cycle. It was noted that response was not exclusively dependant on linear shrinkage of tumorous lesions, but was more or less related to clearer margins of tumor tissue to surrounding tissues and the occurance of hypodense and cystic areas within the lesions.
The Karnofsky scale in accordance with changes in pain symptoms was determined before start of each cycle.
The histological evaluation of tumor regression, especially in case of extensive tumor necrosis, was supposed to detect remaining rests of vital tumor cells as a source of later relapse which were not detectable by means of clinical parameters like markers or radiological diagnostic methods (CT, ultrasound).

Group II.

This group, without randomization, consisted of patients, who, after the instructional discussion, were reluctant or afraid of invasive procedures like surgery or chemotherapy and whised to have more conservative treatment. Most of them received pain medication, apart from epidural catheters in severe cases, and parenteral nutrition.

Results

Group I. In all 20 patients 8–10 weeks after the beginning of therapy a second look surgery was performed. 8/20 patients turned out to be resectable. In one patient there was no more tumor tissue detectable although primary surgery had shown an infiltrating tumor at the head of the pancreas of 10 cm in diameter. This patient survived 35 months and died from late pulmonary metastases. In four patients a resection of the corpus and tail of the pancreas could be performed (1 R0, 2 R1). 12/20 patients were non-resectable after regional chemotherapy. For estimation of histological response multiple biopsies were taken from the pancreatic tumor and sur-

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Table II. Response rates after celiac axis infusion (Mitoxantron chemoembolisation and MMC chemofiltration).

Clinical response (CT, Tumor marker, Karnofsky Index)			Histological response	
	n-Pat.	%	n-Pat.	%
CR	4/20	(20%)	4/20	(20%)
PR	12/20	(60%)	13/20	(65%)
MR	3/20	(15%)	1/20	(5%)
NR	1/20	(5%)	2/20	(10%)

rounding tissues as well as liver metastases. In 4/20 patients no more tumor tissue could be detected in the biopsies, 13/20 patients showed a partial remission (> 50% regression), in 1/20 patients a minor response was noted and two patients had to be classified NR (table II). The result of clinical response, taking into account tumor markers, CT and Karnofsky scale, also showed 4/20 CR (20%). A partial remission was observed in 12/20 patients, MR in 3/20, NR in one patient.

Survival

The mean survival time of all 20 patients amounted to 12 months, median survival was 10.2 months. One patient died after 35 months. One patient is living without evidence of disease for 28 months and one patient – formerly with liver metastases – for 21 months. A further patient is living now for 20 months with recurrence occuring after 15 months. Therapy was already repeated, consisting of celiac axis infusions.

Quality of life

Celiac axis infusional chemotherapy does not influence the quality of life to a significant extent. Turbulences in the celiac axis blood stream, caused by catheter infusion, result in a somewhat homogenous distribution of the drug, thus avoiding laminar flow and the "drug streaming" phenomenon which might cause spot like high drug concentrations inducing ulcers through side branches like the gastroduodenal or gastric arteries. Patients report mild gastritis and lack of appetite at the most. Irritation of the pancreas occurs only to a small extent, showing elevation of the lipase not higher than about 600 U/l over about one week.
A decrease or resolution of pain with reduction of pain medication is generally observed within a few days after the beginning of therapy. As a consequence the Karnofsky Index is improved.

Group II

In the group of patients treated conservatively a short term relief of symptoms was achieved. However, the clinical situation worsened continuously, at the end rapidly, and median survival was 1.5 months.

Discussion

Non-resectability of pancreatic cancer at the time of diagnosis in most cases, poor chances of curative resection in general (4, 12, 21, 22) and few influence of screening methods for early disease detection have promoted the opinion to put more effort into improvement of therapeutic measures. Since the early routes of metastasation are mainly confined to the region supplied by the celiac axis, it seems reasonable to target cytostatic drugs through this artery in order to increase local exposure. To our experience and in vitro chemosensitivity testing performed by *Link* et al. (13), pancreatic cancer, too, is subject to a concentration-response behaviour. It has therefore been postulated that cytotoxic infusion of the celiac axis should result in a better local response. A phase II study, performed with this technique by our group, seemed to confirm the hypothesis of improved response and survival. However, there was no randomized or comparative group with or without systemic chemotherapy (1).
In the study presented herein, 20 patients each with nonresectable stage III and IV disease underwent regional chemotherapy versus conservative symptomatic treatment. The group of pa-

tients treated locoregionally showed clear advantages concerning mean survival of 12 months and median survival of 10.2 months versus 1.5 months in the non-treated group. There is the disadvantage of missing randomization, possibly leading to a higher amount of liver metastases in the non-treated group. While observing the clinical course of the disease, however, after therapy the performance scale showed a fast improvement along which a decrease of the clinical parameters at the same time. The nontreated group on the other hand showed a rapid increase of clinical symptoms and decrease of performance and general condition. Obstruction of the extrahepatic bileduct caused by growth of the primary tumor often is suggested to be the cause of death. Therefore disseminated liver metastases in the periphery of the organ must not necessarily be of predominant importance in terms of prognosis. Nevertheless there is a need for a controlled prospective randomized trial comparing regional and systemic chemotherapy.

There is a theoretical and anatomical advantage of intraarterial chemotherapy as compared with internal or external beam radiation, because i.a. therapy is more likely to follow the pathologic-anatomical pathways of metastatic spread other than a fixed quadrant in a field of radiation. Yet, an important prerequisite of homogenous drug distribution is the avoidance of the so-called "drug streaming" phenomenon (7, 20) in a laminar flow system. According our experience this can lead to inhomogenous response in the target area, caused by just a little change in the position of the tip of the angiographic catheter. The totally implantable Jet Port Allround celiac axis catheter (PfM, Cologne, Germany) with its fixed tip reduces this risk substantially. In primary surgery, due to incontrollable tumor masses at the celiac axis, implantation of this catheter can be rather complicated or impossible, but is more likely to be feasible after induction chemotherapy at the time of second look surgery.

In sensitive tumors primarily delayed or second-look surgery after induction chemotherapy may lead to resectability. This was observed in 8/20 cases. Furtheron second-look surgery facilitates classification of response, since tumor markers and radiologic methods like CT-scan and ultrasound fail in the case of small residual tumor lesions that might be a source of later recurrence. It has been observed that the course of tumor markers was in clearer coincidence with histologic findings than CT-scan, since only in 2/4 CR patients CT showed complete disappearance of all lesions, in 1/4 patients each either tumor formations shrank to approximately 20–30% of the initial measures or cystic transformation of the former tumorous lesion could be seen. In those cases markers had turned down to normal.

The therapeutic design mentioned in this study seems to have advantages but certainly can be optimized. There is a high open potential of local increase of the total dose of drugs and central venous detoxification by means of chemofiltration (3, 14). The increase of the total dose of spherex starch microspheres offers a further very potent tool to exploit the potential of cytotoxic drugs and thus achieve an optimal local exposure. Areas supplied by other visceral branches than the celiac axis should also be taken into account as a possible way of metastasation. Therefore the superior mesenteric artery might gain more importance as soon as potentially distant metastases should be treated prophylactically, moreover since pancreatic cancer potentially metastasizes throughout the peritoneal cavity.

In case a randomized study shows an advantage of regional chemotherapy the most logical indication would be studies in early stages of resectable or borderline resectable tumors treated by means of induction or adjuvant regional chemotherapy.

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