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Review

Regional chemotherapy in the treatment of advanced pancreatic cancer — is it relevant?

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Abstract

The treatment of pancreatic cancer is still problematic for physicians. Only 15% of patients present with resectable tumours, and systemic chemotherapy is of limited effectiveness. In order to achieve higher local drug concentrations in the tumour without causing the side-effects of a comparable level of systemic treatment, regional chemotherapy has been introduced as an alternative treatment. Several techniques have been developed over recent years, these include: celiac axis infusion (CAI), CAI with microspheres or haemofiltration, aortic stop flow (ASF) and isolated hypoxic perfusion (IHP). Whilst several authors have reported improved response rates and a prolongation of median survival time, these results have not been confirmed by others. In addition, the incidence of side-effects and the rate of technical complications have been reported to be high during regional chemotherapy. Except for a single trial containing 14 patients, no randomised trial comparing systemic and regional chemotherapy has been conducted. For these reasons, none of the reported treatment regimens can be considered to be standard treatment and in order to evaluate, if regional chemotherapy is indeed superior to systemic chemotherapy, randomised trials must be conducted.

Keywords: Regional chemotherapy; Pancreatic cancer; Celiac axis infusion; Aortic stop flow; Isolated hypoxic perfusion

1. Introduction

Cancer of the pancreas has the poorest prognosis of all gastrointestinal tumours, with a median survival of approximately 3 months from diagnosis [1]. Less than 20% of affected patients survive 1 year and less than 3% survive longer than 5 years [2]. In 1990, more than 40 000 patients died from pancreatic cancer in the European Union alone [3].

At the present time, the only curative treatment is surgery. However, only approximately 15% of the affected patients are diagnosed at a disease stage in which the tumour is resectable. Even after an apparently curative resection, the 2-year survival rate is only approximately 15% [4]. The majority of patients present with tumours extending beyond the gland with local infiltration, distant metastases or even peritoneal carcinomatosis; regional lymph nodes are very often affected, even if the primary tumour is small and technically resectable [1].

Systemic chemotherapy has been reported to be marginally effective in the palliative treatment of pancreatic cancer, although no treatment protocol has reproducibly demonstrated response rates of more than 20%. The agent most frequently used in systemic chemotherapy is 5-fluorouracil (5-FU). Using 5-FU-containing regimens, response rates of less than 20% and a median survival of up to 6 months have been demonstrated [5]. With regard to response rates and median survival, other therapies such as mitomycin C (MMC), cisplatin, ifosfamide, streptozotocin and gemcitabine as well as combination chemotherapy have not proven to be superior to single-agent 5-FU treatment [5]. In fact, only gemcitabine has proven to be superior to single-agent 5-

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FU treatment as far as quality of life is concerned [6]. Recent investigations have focused on docetaxel and CPT-11 in the systemic treatment of pancreatic cancer, but results from these trials have not yet been reported.

A possible explanation for these unsatisfying results of systemic chemotherapy is the existence of the multidrug resistance gene (*MDR1*). This gene, coding for a membrane protein (*P*-glycoprotein) is expressed in most pancreatic carcinoma cells. It is because of higher levels of *P*-glycoprotein that the intratumoral concentration of the applied drugs is decreased by the presence of an increased efflux out of the tumour cells [5,7].

According to Hryniuk and colleagues' hypothesis, tumour response to chemotherapy can be improved by an increased intratumoral drug concentration [8]. Therefore, as with regional chemotherapy of hepatic metastases, the intra-arterial application of cytostatic drugs to the pancreas seems to be an attractive option [9,10]. The advantage of the intra-arterial application is the presence of an acceptable systemic drug concentration during high-dose regional chemotherapy.

This article reviews all available English and German spoken publications, which were cited in the Medline database of *Pubmed* until September 1999.

2. Anatomical basis for regional chemotherapy of pancreatic cancer

The arterial blood supply to the pancreas is provided by branches of the truncus coeliacus and the superior mesenteric artery. The distribution of the pancreatic blood supply has been investigated by Donatini and colleagues in 1992 in a postmortem evaluation. In 33% of the cases examined, a strictly separated blood supply to the head and the rest of the pancreas was found. In the majority of the cases, anastomoses between the pancreatic head and the rest of the pancreas were discovered [11]. In all cases, the branches of the truncus coeliacus provided sufficient perfusion for the whole pancreas. This means that the application of cytostatic drugs into the truncus coeliacus always affects the entire pancreas, whereas a more selective application will not always provide sufficient perfusion of the tumour. In addition, the majority of patients present with hepatic metastases, these are perfused via the hepatic artery, arising from the truncus coeliacus. For this reason, a drug infusion into the aorta or the truncus coeliacus would seem to be advantageous.

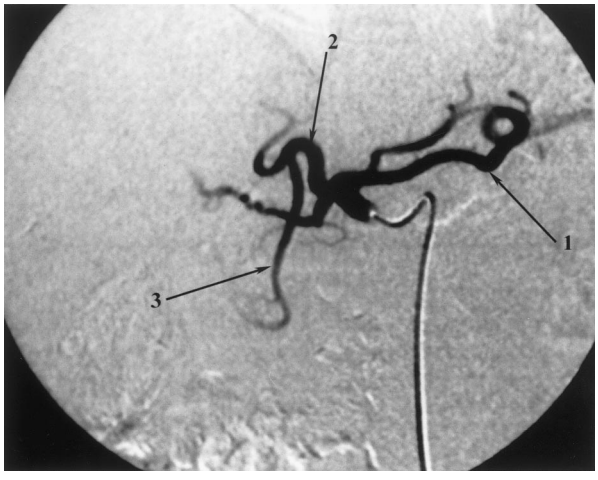

Fig. 1. Angiographic image of celiac axis infusion (CAI) (1, splenic artery; 2, hepatic artery; 3, gastroduodenal artery).

3. Techniques for regional chemotherapy of pancreatic cancer

During recent years several techniques for regional chemotherapy of the pancreas have been developed.

3.1. Celiac axis infusion (CAI)

An angiographic catheter is inserted into the femoral artery and advanced into the abdominal aorta (Fig. 1). Under angiographic guidance, the catheter is placed in the truncus coeliacus and connected to the infusion device; it is usually left in this position for the entire cycle of chemotherapy. With CAI, the pancreas and the liver, which is the most common site of metastasis from pancreatic cancer, can be perfused with high-dose chemotherapy.

3.2. Celiac axis infusion (CAI) with microspheres

The intra-arterial injection of microspheres during CAI has been reported as having the advantage of a decreased washout of the infused drugs. In addition, the embolisation with microspheres results in a decreased blood supply to the tumour having the overall effect of intratumoral hypoxia, resulting in tumour necrosis and possible increased cytotoxicity of the infused drug.

3.3. Celiac axis infusion (CAI) with haemofiltration

To reduce systemic drug exposure during CAI, an additional double-lumen filtration catheter can be inserted via the femoral vein into the inferior vena cava (IVC). This catheter is positioned above the hepatic veins and is connected to an extracorporeal filtration system, which extracts the arterially infused drug from the venous blood.

3.4. Aortic stop flow (ASF)

A double lumen balloon catheter is transfemorally inserted into the abdominal aorta and placed above the

truncus coeliacus. Drug infusion via the catheter is started after inflation of the balloon. The flow reduction in the abdominal aorta and the truncus coeliacus after the inflation of the balloon results in an increased drug exposure time for the tumour. In addition to this, hypoxia occurs in the region distal to the balloon catheter; this can also increase the efficacy of the infused drug. However, the drawback to this is that the entire abdomen and the lower extremities are also exposed to the cytostatic drugs during ASF.

3.5. Isolated hypoxic perfusion (IHP)

Under general anaesthesia, two double lumen balloon catheters are transfemorally inserted into the abdominal aorta and the IVC (Fig. 2). These catheters are advanced above the truncus coeliacus and above the hepatic veins, respectively, and are connected to an extracorporeal roller pump. Torniquets on the thigh exclude the legs from chemoperfusion and provide for an isolated perfusion of the abdomen. After inflation of the torniquets and the balloon catheters, the perfusion of the abdomen is provided by the extracorporeal roller pump. The chemotherapeutic drugs are infused into this isolated compartment over a period of 5 min with the perfusion being maintained over a period of 20–25 min.

4. Pharmacological basis for regional chemotherapy of pancreatic cancer

The advantage of the selective application of chemotherapeutic drugs to the tumour is that high regional drug concentrations can be obtained without the ensuing side-effects of a comparable systemic treatment. A higher level of local drug exposure results in a higher uptake of the cytostatic drugs into the target tissue [8]. The regional concentration of the cytostatic drug has an inverse relationship with the regional arterial blood flow: i.e. the lower the blood flow, the higher the regional drug concentration and vice versa. It is for this reason that microspheres are intra-arterially administered to reduce the blood flow in the target tissue [12]. In addition, the systemic drug concentration is decreased because of a reduced drug washout from the tumour. A similar effect can be achieved by using the ASF technique. Apart from direct pharmacological advantages of an intra-arterial infusion, the systemic drug concentration of the infused drugs is decreased by the hepatic metabolism. For these reasons, drugs with a high hepatic first-pass or total body clearance (TBC) are preferable for use in regional chemotherapy.

The drugs which are frequently used for regional chemotherapy of pancreatic cancer are MMC, mitoxantrone, 5-FU, folinic acid, cisplatin and epirubicin. Some drugs, such as MMC and doxorubicin have been reported to be more effective under hypoxic conditions [13] and are, therefore, preferably used in ASF and IHP. Because of its high TBC, gemcitabine seems to be suitable for an intra-arterial application [14].

Previous studies have demonstrated the pharmacokinetic advantage of an intra-arterial over an intravenous application [15,16]. In an animal model, isolated perfusion of the abdomen exhibited the highest local drug concentrations, further to this, the local concentration of the cytostatic drugs was 3–6-fold higher than after a selective intra-arterial infusion (CAI), and 16-fold higher than after an intravenous application of the same dose. In these trials, systemic drug levels occurred during IHP, indicating that the perfused compartment is not completely isolated [15,17]; an almost complete isolation was only obtained after ligation of all the non-gastrointestinal branches of the abdominal aorta [15].

Pharmacokinetic studies of IHP in humans have confirmed these data. In two trials of IHP in pancreatic cancer, the drug concentration in the perfusate was found to rapidly decrease during perfusion with systemic drug levels occurring 5 min after the application of MMC. After 15 min of perfusion, the concentrations in the perfusate and in the systemic circulation were equal [18,19].

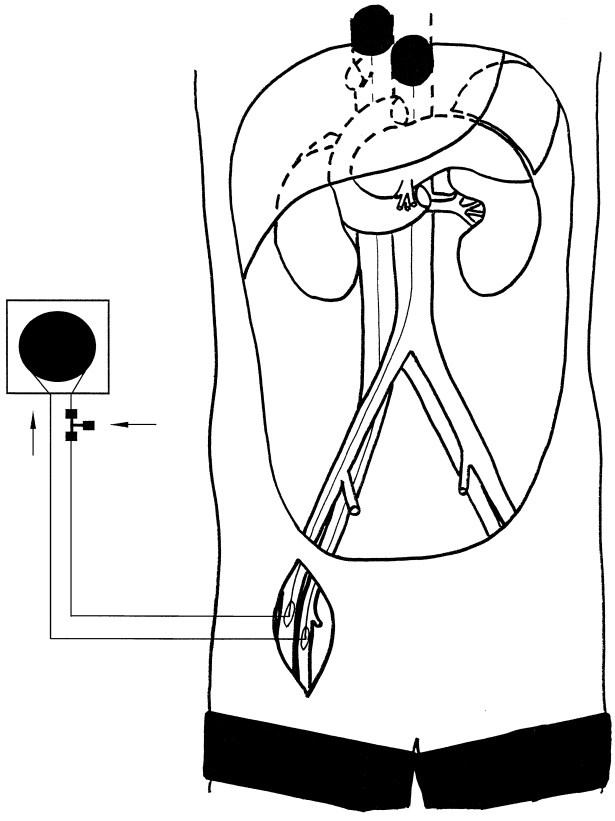

Fig. 2. Schema of isolated hypoxic perfusion (IHP).

5. Results

The results of regional chemotherapy for pancreatic cancer are displayed in Tables 1 and 2. According to the definition of the World Health Organization (WHO), the objective response rate in Tables 1 and 2 includes the reporting of complete and partial remissions. A complete remission is defined as the disappearance of any evidence of tumour (either primary tumour or metastases). A partial remission is defined as a minimum of a 50% reduction in tumour size without the reappearance of any new lesions [20]. Only regimens that reproducibly demonstrate response rates of greater than 20% can be considered an effective treatment regimen for this tumour type [20]. Toxicities, according to WHO [20] or National Cancer Institute (NCI) [21] standard criteria, and technical complications resulting from regional chemotherapy of pancreatic cancer are summarised in Table 3.

5.1. CAI

Hafström and colleagues, Smith and associates and Theodors and coworkers reported median survival of 5–7.5 months after intra-arterial chemotherapy in the 1980s [22–24] the differing response rates being explained by the differing response criteria. Given that computed tomography (CT) was not universally available, different criteria such as angiographic or radioactive examinations were used to define a tumour response (Table 1).

Aigner and colleagues treated 26 patients with non-resectable pancreatic cancer using intra-arterial combination chemotherapy [25]; using this method, only mild side-effects in the absence of local toxicity were reported. 17 of the 26 patients (65%) responded to the treatment as measured by tumour markers only. The objective response rate evaluated according to the WHO criteria was not reported.

In their trials at the University of Ulm, Link and colleagues and Gansauge and associates evaluated CAI using a 5-day regimen [26,27]. On the first day of each treatment cycle an infusion catheter was angiographically placed into the truncus coeliacus and left in position until the end of the cycle. A partial remission was observed in 6 patients (19%) with a median survival of 7.5 months. Whilst Gansauge and colleagues reported primarily the presence of mild side-effects (WHO Grades I, II), Link and associates reported that approximately 10% of the patients suffered from WHO Grade III side-effects, mostly gastroduodenitis. Some of the treated patients had carcinoma of the pancreas other than adenocarcinoma, for example, anaplastic carcinoma or cystadenocarcinoma.

Maurer and associates, using a similar protocol as Link and associates reported that only 1 patient (8%) responded to the treatment [28]; the response was documented by CT-scan and by the tumour-marker CA 19-9. The median survival time in this trial was shorter than that in the previous trials. The most frequent side-effects were those affecting the intestine and the bone marrow, with 4 patients (33%) suffering from WHO Grade III side-effects. Because of these disappointing results, this trial was terminated at an earlier time point than planned.

Of the 12 patients treated by Gebauer and associates, 4 patients responded to the treatment protocol [29], one of these patients exhibited a complete remission. The response criteria were not reported in this publication. The most frequently observed side-effects were also those affecting the gastrointestinal tract and included nausea and vomiting, as well as the bone-marrow effects such as leucopenia. All side-effects were graded as WHO Grades II–III.

Using a protocol adapted from a previously published protocol [30], we treated 17 patients by CAI using a combination of the intra-arterial application of MMC/gemcitabine and a systemic infusion of gemcitabine. On day 1, 8.5 mg/m^2 MMC and 500 mg gemcitabine was applied intra-arterially on days 8 and 15, 500 mg gemcitabine was applied systemically. 5 patients (29%) demonstrated a partial remission, and the median survival was 10 months. WHO Grade III side-effects were registered in 7 cases, with the most frequently observed side-effect (WHO Grade III) being a thrombocytopenia ($n = 3$).

Muchmore treated 32 patients with CAI plus a venous haemofiltration [31]. In this study an objective response rate of 38% and a median survival of 9–13 months was obtained in patients with advanced pancreatic cancer. The reported side-effects were mild, the most frequent complication was gastroduodenitis, and 3 patients developed a deep vein thrombosis following the treatment.

5.2. ASF

Given that the results of several trials using ASF have only been published as abstracts, a further analysis and comparison of these trials is not possible. However, it has been reported in a review article that the tumour response rate was approximately 90% and that the median survival was approximately 9.8 months (Table 2) [32]. The response to therapy was evaluated by the presence of tumour markers and by histological examinations.

5.3. IHP

Fiorentini and associates treated 20 patients using IHP (Table 2) [33]. 10 patients (50%) were found to respond to the treatment; the median survival was not

Table 1
Results from trials on celiac axis infusion (CAI) in the palliative treatment of pancreatic cancer

Author [Ref.]	No. of patients	Treatment protocol	Schedule	Response criteria	Response rate (%)	Median survival (months)
Hafström [22]	19	5-FU 10 mg/kg BW	Daily for 1 month	Angiography	0/19	7.5
Smith [23]	47 9 4 3	5-FU 15 mg/kg BW/day Cyclophosphamide 1 g, vincristine 2 mg, methotrexate 50 mg Cyclophosphamide 1 g, vincristine 2 mg Vincristine 2 mg	Over 5 days	–	–	5
Theodors [24]	19	5-FU 800–1000 mg/m^2, streptozotocin 500–600 mg/m^2 Doxorubicin 15–20 mg/m^2, MMC 4–6 mg/m^2	4-weekly intervals	CT	8/19 (42)	5.2
Aigner [25]	26	MMC, CDDP, 5-FU	Daily 1-h infusion	Tumour markers	17/26 (65)	–
Link, Gansauge [26,27]	32	Day 1: mitoxantrone 10 mg/m^2 Days 2–4: folinic acid 170 mg/m^2 5-FU 600 mg/m^2 over 120 min Day 5: cisplatin 60 mg/m^2	4-week intervals up to progression or 11 cycles	CT	6/32 (19)	7.5
Gebauer [29]	12	Spherex 300–600 mg + epirubicin 40 mg/m^2, followed by folinic acid 500 mg/m^2 and 5-FU 2.4 g/m^2	4-week intervals	–	4/12 (33)	6.8
Maurer [28]	12	Day 1: mitoxantrone 10 mg/m^2 Days 2–4: folinic acid 170 mg/m^2 5-FU 600 mg/m^2 Day 5: cisplatin 60 mg/m^2	6-week intervals up to disease progression	CT tumour markers	1/12 (8)	6
Muchmore [31]	32	MMC 20–24 mg/m^2, 5-FU 500–700 mg/m^2 + haemofiltration	4-week intervals up to disease progression	CT	12/32 (38)	UICC II/III: 13 UICC IV: 9

5-FU, 5-fluorouracil; BW, body weight; MMC, mitomycin C; CDDP, cisplatin; CT, computed tomography; –, not listed in original publication.

Table 2
Results from trials on aortic stop flow (ASF) and isolated hypoxic perfusion (IHP) in the palliative treatment of pancreatic cancer

Author	No. of patients	Treatment protocol	Schedule	Response criteria	Response rate (%)	Median survival (months)
Aigner [32]	14[a]	1 cycle: CAI with 5-FU (2×1000 mg), MMC (14 mg), CDDP (2×50 mg) 2 cycle: ASF with MMC (20 mg)	–	–	7/14 (50)[b]	9.8[c]
	14[a]	IHP with MMC (20 mg)	–	–	8/14 (57)[b]	
Fiorentini [33]	20	MMC 25 mg/m^2 over 5 min infusion, perfusion over 22 min	–	CT	10/20 (50)	3–12[d]
Lorenz [34]	17	IHP with MMC (40 mg)	6-weekly intervals up to progression	CT	0/17	4.2
Gebauer [29]	17	IHP with MMC (20 mg)	4-weekly intervals	–	3/17 (18)	4.5

CAI, celiac axis infusion; ASF, aortic stop flow; IHP, isolated hypoxic infusion; MMC, mitomycin C; 5-FU, 5-fluorouracil; CDDP, cisplatin; CT, computed tomography. –, not listed in original publication.
[a] 48 patients entered the trial, 28 of the patients were evaluated.
[b] Clinical response, not further defined in original paper.
[c] Median survival of both treatment groups.
[d] 3 months for non-responders, 12 months for responders.

reported from this trial. However, responders were reported to have a median survival of 12 months, with the median survival of non-responders being only 3 months. In all, 9 cases (45%) of WHO Grade III toxicities were registered. In addition, there were 5 cases of technical complications of which 4 cases were anaesthesiological complications occurring during IHP.

Aigner has reported on the high response rates and the prolongation of median survival in patients with metastatic pancreatic cancer that was confined to the abdomen [32]. Patients with peritoneal carcinomatosis were reported not to benefit from regional chemotherapy. The side-effects and toxicities were not named in this publication, and approximately 50% of the treated patients had not been evaluated.

Table 3
Toxicity, according to WHO standard criteria [20], and technical complications resulting from regional chemotherapy of pancreatic cancer

Author [Ref.]	Toxicity					Technical complications					
	Gastrointestinal		Haematological		Others	Catheter associated	Infection/ abscess	Arterial thrombosis	Aneurysm	Anaesthesiological	Others
	Grade I–II	III–IV	I–II	III–IV	I–IV						
Hafström [22]	–	–	–	–	–	8	–	13	–	–	2[a]
Smith [23]	+	+	+	+	–	11	4	1	1	–	–
Theodors [24]	+	+	+	+	–	9	1	3	–	–	
Aigner [25]	+	–	–	–	+[b]	1	–	–	–	–	–
Gansauge [27]	64	–	10%	1	3[c]	3	–	–	1	–	2[d]
Link [26]	114	21	19	2%	–	4	–	–	2	–	–
Gebauer [29]	+	+	+	+	–	–	–	–	–		–
Maurer [28]	12	1	10	2	6[e]	–	–	–	–	–	–
Muchmore [31]	+	+	+	+	–	–	–	–	–	–	3[f]
Aigner [32]	–	–	–	–	–	–	–	–	–	–	–
Fiorentini [33]	7	3	–	6	–	–	–	–	–	4	1[f]
Lorenz [34]	28[g]	5[g]	22[g]	2[g]	51[h]	0	2	0	0	1	5[f]
Gebauer [29]	–	+	–	+	–	–	–	–	–	–	–

Catheter-associated complications are catheter dislocation and occlusion.
[a] Cerebral emboli.
[b] Pancreatitis.
[c] Fever.
[d] Arterial injury.
[e] Renal toxicity (WHO Grade I) in 5 patients, fever (WHO Grade III) in 1 patient.
[f] Venous thromboses.
[g] NCI criteria [21].
[h] Multiple side-effects.
–, Not listed in original publication.
+, Not defined according to WHO or NCI standard criteria.

Gebauer and colleagues treated 17 patients using IHP, of these, 3 patients (18%) responded to treatment with a median survival of 4.5 months. The most commonly observed side-effects were nausea, emesis and diarrhoea, all of the side-effects were classified as WHO Grades III–IV [29].

In our own trial on isolated hypoxic perfusion of the abdomen, none of the patients were found to respond to treatment, the median survival was 4.2 months, similar to that of the untreated patients. This regimen resulted in severe side-effects and perioperative complications [34]. The majority of side-effects affected the gastrointestinal tract resulting in nausea, emesis and diarrhoea, with 40% of the patients suffering from severe side-effects (NCI $\geqslant$ Grade III). In addition, 5 patients (29%) suffered a deep vein thrombosis following IHP.

6. Discussion

Pancreatic cancer is considered to be a drug-resistant disease with a dismal prognosis. Since treatments utilising 5-FU, MMC, ifosfamide and streptozotocin have all demonstrated limited antineoplastic activity as single agents or in combination chemotherapy, 5-FU has been regarded as being adequate as a palliative approach for advanced pancreatic cancer [5]. Recently, it has been shown that gemcitabine is superior to 5-FU treatment with respect to the achievable quality of life and median survival [6]. Therefore, most oncologists regard gemcitabine as the reference treatment for advanced pancreatic cancer.

It has been suggested that higher local drug concentrations must be applied to the tumour in order to overcome drug resistance, without increasing systemic toxicity [8]. This is the rationale for regional chemotherapy of pancreatic cancer.

Despite disappointing results in the early 1980s [22–24], in recent years, several clinicians have reported improved response rates and a prolongation of the median survival times following regional chemotherapy of pancreatic cancer [26,27,31–33].

Although pharmacological evaluations on CAI have not been performed, this technique has been used in several trials. In addition, mitoxantrone has been frequently used in CAI, although this drug has no proven effectiveness in the systemic treatment of pancreatic cancer. This technique has been reported to be feasible with an acceptable level of side-effects. Several authors have reported that the use of this technique improved the response rates and resulted in a prolongation of the median survival. However, CAI is conducted in an inpatient setting with the duration of each treatment cycle lasting 5–7 days. During this regimen, patients must stay in bed for the complete treatment period, due to the intra-arterial catheter remaining in place in the truncus coeliacus. Patients suffering from pleural or peritoneal carcinomatosis, as well as patients with pulmonary metastases, do not benefit from CAI, since these tissues are not arterially supplied from the truncus coeliacus. Because of the promising clinical results of CAI in the palliative treatment of pancreatic cancer, CAI has also been introduced for the adjuvant treatment of pancreatic cancer [35].

An interesting alternative treatment is the combination of CAI and systemic chemotherapy. An overnight stay in hospital at 3-weekly intervals for CAI, as well as a weekly systemic treatment, is reasonable to expect and is well tolerated by patients. Preliminary, unpublished analyses of this trial demonstrate that there are interesting clinical results and that they have an acceptable level of reduced quality of life. After this protocol has reliably proven efficacy in a phase II trial, a randomised trial should be performed, comparing this protocol with the systemic application of MMC/Gemcitabine.

ASF and IHP are even more invasive techniques than CAI. IHP requires a general anaesthesia and an average stay of 7 days in hospital. Because of the severe haemodynamic and pathophysiological changes occurring during these therapies, a postoperative observation in intensive care units is often necessary [18]. Although many authors have reported excellent clinical results following ASF and IHP therapy, two prospectively planned phase II trials were unable to confirm these data [29,34]. Because of the severe side-effects, which mostly affected the intestine with diarrhoea and emesis, both regimens, ASF and IHP, have a negative impact on quality of life. On the basis of our own experiences, we no longer conduct trials using IHP, and we cannot recommend this technique for use in patients with unresectable pancreatic cancer.

There are several reasons for the difference in the results of regional chemotherapy for pancreatic cancer. Most of the trials were only performed as pilot studies with selected, small and non-homogeneous treatment groups with locally advanced disease. These trials were performed without any prior planning as to the size of the trial. In addition, different definitions of and parameters for a tumour response were used. It is obvious that results from trials that are based on tumour markers only, are not comparable with trials that are based on CT or magnetic resonance imaging (MRI) scans as parameters of tumour response.

Moreover, imaging of the primary tumour by CT or MRI is extremely difficult. Due to its retroperitoneal location and its close relationship to several organs, the differentiation of tumour tissue from surrounding inflammatory tissue, tumour desmoplasia, fibrosis, necrosis or poorly opacified bowel is very difficult [36]. As a result, tumour measurements are often subjective, and the definition of the objective tumour response remains problematic. However, CT and MRI are

suitable for the detection of local recurrences and distant metastases.

For these reasons, the time to progression and the median survival are better endpoints for trials on advanced pancreatic cancer [36]. However, to compare the results of clinical trials using different chemotherapeutic regimens, internationally accepted definitions of tumour response have to be used [20].

None of these regimens has reproducibly proven to be superior to systemic treatment. Response rates of greater than 30% and a median survival time of more than 6 months have also been reported from the phase II trials on systemic chemotherapy for pancreatic cancer [5]. However, these results have not been confirmed by randomised trials. Except for one trial, which was terminated after the treatment of 14 patients, no randomised trial has yet been performed on regional chemotherapy for pancreatic carcinoma [37].

Because of the unsatisfying response rates of chemotherapy, the aim of palliative treatment in patients with pancreatic cancer should be the improvement in quality of life of the affected patients. It is questionable whether the reported improvement in survival after regional chemotherapy can be accepted at the expense of a reduction in the quality of life, caused by repeated stays in hospital and, especially after ASF and IHP treatment, the ensuing severe side-effects. In addition, the biology of pancreatic cancer with its early and fast systemic metastasis, suggests against the regional application of cytostatic drugs. Finally, the symptoms of local infiltration, such as back pain or biliary obstruction, might be influenced by regional chemotherapy. To date, no clear data have demonstrated that regional chemotherapy has a positive impact on these symptoms.

In summary, none of the above treatment regimens can be considered to be a standard treatment and should not be performed outside controlled clinical trials. If patients with advanced pancreatic cancer benefit from regional chemotherapy, this must be assessed in randomised trials.

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