Intravenous and intra-arterial chemotherapeutic possibilities in biliopancreatic cancer

C.J. van Groeningen
Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, the Netherlands

Summary
Chemotherapy of carcinomas of the pancreas and biliary tract has always been of limited value. Pancreatic cancer is well known for its aggressive nature, poor prognosis and resistance to antineoplastic agents which are effective in other solid tumors. 5-Fluorouracil has long been the mainstay of the treatment of pancreatic cancer, although the response rate to this agent is < 10% and the influence on survival and quality of life is negligible. Combination chemotherapy in pancreatic cancer adds to the side effects of treatment, but has had no proven effect on effectiveness. The only new anticancer drug of which an improvement in clinical benefit has been indicated on the basis of randomized clinical research, is gemcitabine, although the magnitude of improvement is limited. Due to the rarity of tumors of the biliary tract, the data on the effect of chemotherapy in this disease is sparse but does not suggest that it leads to superior results than supportive care alone. Likewise, no literature exists supporting the routine application of regional chemotherapy infusion in these type of tumors.

Key words: biliary tract cancer, chemotherapy, 5-fluorouracil, gemcitabine, intra-arterial chemotherapy, pancreatic cancer, regional chemotherapy

Pancreatic cancer

Intravenous chemotherapy
The great majority of the patients with pancreatic cancer can only be treated in a palliative setting and chemotherapy is the only modality of which this can be expected. The course of pancreatic cancer is often very aggressive and only 1-4% of the patients are still alive 5 years after the diagnosis has been made [1]. Traditionally, clinical studies on chemotherapy in pancreatic cancer have almost always yielded very low response rates while this treatment had only little impact on the survival as well as on the quality of life. Occasionally higher response rates have been observed but almost invariably, these results could not be reproduced when such a study was repeated. The antineoplastic agent most studied and applied in the treatment of pancreatic cancer is 5-fluorouracil (5-FU). Reported response rates in the past have varied considerably, ranging from 8-85%, however, there is consensus between medical oncologists that the true objective response rate of 5-FU is well below 10% and that this treatment does not influence the overall survival of the patients treated [2]. Because biochemically modulated 5-FU resulted in modest improvement of the treatment results in colorectal cancer this approach has also been tried in pancreatic cancer. However, results in pancreatic cancer were disappointing; clinical trials in which 5-FU was combined with folinic acid, or with folinic acid plus interferon-α gave similar response rates and durations of survival than 5-FU alone [3,4]. Although response rates of combination chemotherapy, mostly consisting of 5-FU, doxorubicin, mitomycin C, streptozocin and other agents were higher than of 5-FU alone, this was achieved at the cost of considerably more toxicity while survival duration was not increased [5,6]. Numerous clinical trials have been conducted in pancreatic cancer investigating the role of new anticancer agents. With very few exceptions the results of these trials have been negative. New agents with reported activity include docetaxel [7] and 9-nitrocamptothecin [8]. However, these agents have as yet been studied in only small numbers of patients and their activity has to be confirmed in follow up trials. A novel agent which received the most attention in the recent past is gemcitabine, a nucleoside analog, structurally related to cytarabine. Usually, gemcitabine, 800 - 1250 mg/m2 is administered i.v. weekly for 3 consecutive weeks followed by 1 week rest, every 4 weeks. An initial phase II study noted partial responses in 5 of 42 patients [12%] [9]. Although gemcitabine did not result in a higher rate of objective responses, it was noted that some patients experienced improvement in symptoms and performance status. This was subsequently defined as "clinical benefit response" (improvement in pain, performance status and weight). In a randomized study in 126 patients, gemcitabine was compared with 5-FU [10]. In the gemcitabine arm, 24% of the patients had clinical benefit, while only 5% of the patients randomized to 5-FU showed this feature. Objective response rates were very low in both study arms, 5% of gemcitabine-treated patients, and 0% of 5-FU-treated patients. There was also a slight improvement in survival in the gemcitabine arm. The lack of serious side effects is an important characteristic of gemcitabine which is of particular interest in patients with pancreatic cancer who often have rapidly evolving symptoms of their disease. Adding toxicity to disease symptoms is likely to threaten the quality of life, in particular in a disease not sensitive to chemotherapy. As expected, gemcitabine is currently being combined with other agents aiming at better treatment results in pancreatic cancer. Preliminary results suggest that the combination of gemcitabine and 5-FU may be somewhat more effective than gemcitabine alone [11,12].
Arterial chemotherapy

Surgery of pancreatic cancer is often limited by involvement of the tumor of neighboring structures, in particular the celiac and superior mesenteric vessels. In these circumstances, distant metastatic disease often is still absent. Therefore, the question has been raised whether arterially delivered chemotherapy in locally advanced pancreatic cancer may be beneficial, as combinations of chemotherapy and radiotherapy, either as the only treatment or as neo-adjuvant therapy, have failed to improve the results in this setting [13,14]. Data on arterial chemotherapy in pancreatic cancer are very limited. Celiac axis infusion chemotherapy was studied in 12 patients with advanced non resectable pancreatic cancer [15]. Mitoxantrone, 5-FU + folic acid, and cisplatin was administered by trans femorally placed catheters. A mean number of 2.6 cycles of this combination chemotherapy was given. The results were disappointing; only one patient had a partial response, four had stable disease, while 7 patients showed progressive disease. The median duration of survival was 8.5 months in stage III patients and 5 months in stage IV patients. The same approach of celiac axis infusion was conducted by Muchmore et al. [16], in 12 patients. This was combined with hemofiltration in the vena cava. Five of the patients had an arterial access system implanted, while the other 7 patients had an angiographically placed arterial catheter. The antineoplastic agents applied were mitomycin C (20-24 mg/m²) and 5-FU (500-700 mg/m²). Better results were reported in this latter study; 5 patients had a partial response, 6 had stable disease, while only 1 patient progressed during treatment. Four of the 12 patients underwent a surgical re-exploration, and in one of these patients a curative resection could be performed. Hepatic artery infusion chemotherapy, combined with portal vein infusion has been used as an adjuvant treatment to prevent liver metastases after extended pancreatectomy for pancreatic cancer [17]. This technically sophisticated approach was conducted in 20 patients. 5-FU at a dose of 125 mg/day was administered by both routes during 28 to 35 days. No treatment-related complications were observed. The 3-year survival rate was 54%, while the cumulative rate of death due to liver metastases was only 8%. In the experience of the authors, the results were significantly superior to their results in historical controls. Obviously, it is very difficult to draw any meaningful conclusion of these data on regional chemotherapy in pancreatic cancer; the mentioned studies accrued small numbers of patients in, probably selected patients. It seems unlikely that it is worthwhile to further study this approach in patients with pancreatic cancer before more effective chemotherapy becomes available.

Biliary tract cancer

Intravenous chemotherapy

Biliary tract cancers belong to the rare tumor types. The diagnosis of these tumors is most often made at an advanced stage of the disease, limiting the possibilities of curative resection. Thus, treatment frequently can only be palliative. Obstructive jaundice is often present and can often be managed by stents placed either endoscopically or percutaneously. Pain is also a major symptom in these tumors that negatively influences the quality of life. Experience with palliative chemotherapy is not widespread in biliary tract cancer. Most of the reported studies on chemotherapy contain small numbers of patients. As in the other tumor types of the gastrointestinal tract, fluoropyrimidines are the best studied agents. However, reported response rates are low, and usually below 20% [18,19]. 5-FU in combination with interferon-α, studied in 35 patients, of whom 32 patients were evaluable, showed partial responses in 11 patients (34%). The median time to progression in this group of patients was 9.5 months, while the overall median survival amounted to 12 months [20]. Obviously, it is questionable whether this marginally improved result outweighs the more serious side effects associated with this combination therapy. Mitomycin C, considered by some to be efficacious in the treatment of this disease, resulted in an objective response rate below 10% in a study of the EORTC Gastrointestinal Tract Cooperative Group [21]. Paclitaxel, an active agent in various solid tumor types showed a negative result in a study in patients with unresectable biliary tract cancer. In 15 patients, no objective responses were observed, with only 2 patients having short lasting stable disease [22].

Arterial chemotherapy

In comparison with intravenously administered chemotherapy, the experience with chemotherapy given arterially is even more limited. Because many patients with biliary tract carcinoma have localized disease at presentation, the regional administration of chemotherapeutic agents has a good rationale. The rarity of these tumors limits the conduction of clinical studies on this treatment modality. In a review of several small series of patients in which arterial infusion of chemotherapy was performed, it was reported that partial responses were observed in 15 of 38 patients (39%) [18]. Obviously, these figures are too small to draw conclusions with respect to the potential benefit of this therapeutic approach. More recently, in a somewhat larger group of 27 patients with carcinoma of the gall bladder treated with arterial infusion of mitomycin C, Mäkelä and Kairaluoma [23] reported an overall response rate of 48%. The median survival of 14 months compared favorably with the median survival of only 4 months in historical controls. The treatment appeared to be particular effective for patients in whom the tumor was restricted to the wall of the gallbladder, while it is a common observation that these tumors are usually extended beyond this border. It is also noteworthy that a period of 10 years was required to include the patients in this study. Therefore, no meaningful advises based on literature data, can be given in which patients with biliary tumors arterial infusion chemotherapy should be considered.

References


Correspondence to:
C.J. van Groeningen, MD, PhD
Dept. Medical Oncology
University Hospital Vrije Universiteit
PO Box 7057
1007 MB Amsterdam
the Netherlands