Current chemotherapeutic possibilities in pancreaticobiliary cancer

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Summary
At time of presentation the majority of patients with pancreaticobiliary cancer have locally advanced or metastatic disease which makes them unamenable for curative surgery. In these patients chemotherapy is an option which has gained more support over the past few years. Special problems faced in chemotherapeutic treatment are the patient’s poor condition and the difficulties faced in evaluating response. 5-FU has been the only drug with some efficacy for a long time, but more recently gemcitabine appeared to be more efficient. In locally advanced pancreatic cancer the combination of chemotherapy with radiotherapy has not gained much support. However, studies are implicating better local control with combined treatment and recurrences appear more often at distant sites. In some cases irresectable tumors became resectable. Because of the poor survival after surgery with curative intent, adjuvant and neoadjuvant therapy are becoming important issues. Although studies of adjuvant therapy suggest benefit, research is seriously hampered by poor patient accrual due to the morbidity of pancreaticoduodenectomy. Neoadjuvant treatment may overcome this problem. Until now there has been only modest improvement in the treatment of pancreatic cancer. Hopefully, new treatment modalities such as immunotherapy, gene therapy and antiangiogenic therapy will alter this dismal picture. In biliary cancer the role of chemotherapy is less well defined, since only few studies with low patients numbers have been performed.

Key words: chemotherapy, 5-fluorouracil, gemcitabine, pancreatic cancer, pancreaticobiliary cancer

Introduction
Pancreatic cancer is one of the commonest and most lethal cancers in the Western world with a median survival of approximately 3 months. Surgery, the only curative treatment, is an option in only 10%-20% of patients presenting with this disease, and even after apparently successful resection, patients are rarely cured [1,2]. However, at the time of diagnosis 40% of patients have locally advanced disease (involvement of regional lymph nodes or adjacent tissues) and more than 40% have visceral metastases, most frequently in the liver, which excludes surgery as a realistic option [3]. As a consequence there is a strong need for effective non-surgical treatment modalities in order to treat locally advanced and metastatic disease. Furthermore, with new surgical and radiotherapeutic technics improving loco-regional control, we will face distant metastases being responsible for therapy failure more often and effective systemic treatment will become even more important for prolonging survival [4, 5]. Unfortunately, results obtained with chemotherapy failed to have any appreciable impact on the final outcome of disease and have been the reason for skepticism among oncologists for many years. However, a totally fatalistic approach is not justified, because despite poor overall results a significant proportion of patients do achieve benefit from chemotherapy. In recent years there have been studies documenting a relevant benefit of chemotherapy in patients with advanced disease [6,7].

Specific problems faced in treatment of advanced pancreatic cancer

Supportive care
At presentation patients with advanced pancreatic cancer are generally in poor clinical condition. The combination of pain, malabsorption, gastric outlet obstruction and cachexia seen in many patients will result in a rapid deterioration of their performance score if no vigorous attempts are made to interrupt this vicious circle. Furthermore, if treated with systemic chemotherapy this will make them more susceptible to experience serious toxicity, reducing the possible benefit they would derive from treatment. Therefore, whenever the decision is made to start chemotherapy, treatment should start as soon as possible before further deterioration occurs. And, in order to achieve the maximum benefit for the patient, supportive care becomes an even more important issue. Adequate pain control with the use of chemical splanchectomy or radiotherapy when analgetics fail should be established. When indicated biliary stent placement for the relief of jaundice, or bypass surgery in case of duodenal obstruction should be performed [8]. Because most patients already are suffering of malnutrition and chemotherapeutic treatment at first will do no good to the nutritional status, emphasis should be put on adequate feeding. Enteral nutrition support should be introduced early to prevent further deterioration of the nutritional status. Exogenous pancreas extract can be prescribed to improve the secondary malabsorption syndrome often seen in patients with pancreatic carcinoma [9].

Evaluation of therapy
Response evaluation, especially in locally advanced pancreatic cancer, is often troublesome. Accurate and reliable tumor measurements are often difficult to obtain. In fact, high numbers of patients with unmeasurable disease are a major drawback of many clinical studies performed in pancreatic cancer. Even with computed tomography scanning and magnetic resonance imaging, local structures such as stomach, duodenum, small bowel and normal...
pancreatic tissue may be difficult to distinguish from pancreatic tumor, and tumor compression or invasion of the celiac plexus hard to diagnose. Furthermore, there is often a significant amount of reactive fibrous tissue present in pancreatic cancer, which does not shrink following successful chemotherapy, leading to underestimation of the response. On the contrary, inclusion of inflammatory tissue in measurements can cause overestimation [4,10,11]. As a result, determination of objective response is extremely difficult and unreliable in many patients. Because these difficulties faced in evaluating objective response in pancreatic cancer, new clinical endpoints focusing on disability caused by the tumor have been introduced and ‘clinical benefit response’ defined as ≥ 50% reduction in pain intensity, and/or ≥ 50% reduction in daily analgetic consumption, or ≥ 20% improvement in the Karnofsky performance scale that was sustained for ≥ 4 consecutive weeks, or a weight gain of ≥ 7%, was introduced as endpoint in therapy evaluation [10,12]. Regarding these endpoints, it must be kept in mind that they are subject to the patient’s and clinician’s perception. Furthermore, for correct evaluation of the impact of chemotherapy it is important to adjust clinical benefit to the adverse events [13,14]. Despite these drawbacks, ‘clinical benefit response’ may become an important new tool in evaluating chemotherapy effects, especially in a difficult evaluable malignancy such as pancreatic cancer. Furthermore, CA 19,9 and especially positron emission tomography (PET), a newer imaging technic, may be helpful in the future in distinguishing tumor from fibrotic tissue.

Systemic chemotherapy in pancreatic cancer

Chemotherapy in advanced disease

5-FU and 5-FU-based combination regimens. The most studied agent in pancreatic cancer is 5-Fluorouracil (5-FU) with response rates varying from 8-85%. However, early trials overestimated the efficacy of 5-FU because of inadequate response criteria. At present it is generally believed that the response rate is likely to be below 10% without any impact on quality of life or survival [11]. Biochemical modulation of 5-FU with leucovorin and/or alpha-interferon failed to yield better results [15,16,17,18]. In order to improve this dismal picture, 5-FU has been combined with other drugs having at least some activity in pancreatic cancer. However, despite some encouraging reports of early phase II studies, regimens containing various combinations of mitomycin C, doxorubicin, streptozotocin or cisplatin were found not better than 5-FU alone, and were considerable more toxic [19,20,21,22]. By means of protracted infusion a more favorable therapeutic index of 5-FU may be obtained. In other tumor types such as colorectal cancer protracted 5-FU infusion (PIF) demonstrated to be well tolerated and to significantly enhance the efficacy of this drug. Results of 5-FU PIF in combination with platinum compounds were comparable to the results reported of the earlier mentioned combination regimens but were far less toxic [23,24].

New agents: gemcitabine

The disappointing results obtained with 5-FU and 5-FU combination regimens underlines the need for new active agents in pancreatic cancer. Of the newer agents paclitaxel, docetaxel, topotecan, ZD1694 and temozolomide showed only limited activity with response rates of 5-17% in phase II studies [25,26,27,28,29,30]. On the contrary, gemcitabine, a relatively new nucleoside analog, appeared to have different properties. In a phase II study in 44 patients with advanced pancreatic cancer, despite a low response rate of 11% and a median survival of 5.6 months, important observations were made. In addition to a remarkably high one-year survival rate of 23%, a surprising positive impact of gemcitabine on tumor-related symptoms was found, even in the majority of patients (9 of 14) who had radiological stable disease [31]. The most acceptable explanation for the latter is that gemcitabine causes only minimal tumor shrinkage, however, sufficient for improvement of tumor related symptoms but not evaluable with nowadays imaging technics [10]. Therefore, as mentioned earlier ‘clinical benefit response’ was introduced as primary endpoint to evaluate the efficacy of gemcitabine [12]. In a phase II study of gemcitabine in patients with 5-FU refractory pancreas cancer 63 patients were entered after an initial pain stabilization period. Gemcitabine (1000 mg/m²) was administered as a 30 minute infusion weekly for 7 weeks, followed by one week rest. Thereafter, the drug was given once weekly for 3 out of every 4 weeks. Seventeen patients (27%) achieved a clinical benefit response with a median duration of 14 weeks and a median survival of 3,85 months. The objective response rate was only 10,5% [32]. A randomized trial comparing gemcitabine with 5-FU in first-line treatment, included 126 patients after pain stabilization. Dose and schedule of gemcitabine were identical to those in the mentioned phase II study. 5-FU 600 mg/m² was administered once weekly. Fifteen of 63 patients randomized to gemcitabine experienced clinical benefit response (23,8%) with a mean duration of 18 weeks versus 3 of 63 (4,8%) in the 5-FU treated patients and with a mean duration of 13 weeks. In the gemcitabine group, 5,4% of the patients (3 of 56 patients) with measurable disease had a radiologic response versus none in the 5-FU group (0 of 57 patients). With a 1-year survival of 18%, gemcitabine also showed a modest survival advantage over 5-FU (1-year survival: 2%). However, the median survival in the gemcitabine treated patients was not more than 5,65 months. Both drugs were tolerated well and neutropenia and liver function disturbances were the most important toxicities [33]. Although these are the first studies using clinical benefit response and caution is justified in interpreting the results, gemcitabine seems to be the first agent that has demonstrated improvement of disease-related symptoms and survival in advanced pancreatic cancer. As a result the drug is accepted for first-line treatment at this moment. Studies combining gemcitabine with 5-FU and, especially cisplatin, which showed synergism with gemcitabine in preclinical studies. are ongoing.

Combined modality therapy in locally advanced pancreatic cancer

Loco-regional disease often produces debilitating local symptoms and improved local control would improve quality of life and even permit a possible curative resection in some patients. The Gastrointestinal Tumor Study Group performed a randomized study comparing radiotherapy alone with radiotherapy in combination with 5-FU as radiosensitizing
agent, and a study comparing radiotherapy combined with 5-FU followed by combination chemotherapy (SMF: streptozocin, mitomycin C and 5-FU) versus combination chemotherapy alone. There were no differences between treatments regarding local control of the disease. Significant prolonged survival was found for the combination therapy arm in both studies, although the gain was only a few weeks and can hardly be considered as substantial [34,35]. In contrast, an Eastern Cooperative Oncology Group study did not find significant differences, both regarding local control and survival in patients receiving 5-FU plus radiotherapy or 5-FU alone [36]. As a consequence of all these meager results combined modality treatment did not achieve widespread use. However, more recent phase II studies showed that by chemoradiation, durable local control could be established. Furthermore, downstaging of locally advanced disease occurred and the patients in whom the tumor became resectable had a prolonged survival. The observed pattern of treatment failure outside the radiation field, however, stresses the need for more effective systemic treatment [37,38]. With the introduction of gemcitabine as an active agent in pancreatic cancer, studies combining this agent with radiotherapy are supported by the known radiosensitizing properties of this agent. At this moment phase I studies combining gemcitabine with radiation therapy are ongoing [39,40].

**Adjuvant and neoadjuvant treatment in pancreatic cancer**

The natural history of pancreatic cancer after apparently curative resection, with most patients developing local recurrence and the majority of patients developing liver metastases, implies that adjuvant treatment must be effective against both local recurrence and systemic spread [41,42]. Therefore, chemoradiation appears appropriate in the adjuvant setting. The Gastrointestinal Tumor Study Group randomized patients who underwent curative resection to receive either supportive care or adjuvant treatment consisting of 40 Gy external beam radiotherapy with bolus 5-FU as radiosensitizing agent followed by weekly bolus 5-FU for 2 years, or until recurrence. Because of a disappointingly low patient recruitment, accrual was closed after 8 years. However, the 2-year survival rate for the adjuvant group (21 patients) was 40% versus 20% (22 patients) for the supportive care only group [43]. Survival at 5 year and 10 year was 19% each for the patients who received adjuvant therapy and, respectively, 5% and 0% for the patients in the supportive care arm of the study [42]. In a follow up single-arm study in 30 patients receiving the same adjuvant treatment, similar results were observed [44].

However, a British study (United Kingdom Pancreatic Cancer Group Trials-1) concluded that survival after the GTSG regimen was not improved when compared with surgery alone [41]. A disadvantage of the GTSG regimen is that the start of chemotherapy is delayed for up to three months because of surgery. Using chemotherapy at start may possibly reduce recurrences at all sites. In a randomized study of adjuvant chemotherapy (FAM: 5-FU, doxorubicin and mitomycin C) versus surgery alone, the median survival was 23 months in the chemotherapy group versus 11 months in the control group. However, there was no difference in 3 and 5-year survival rates in both groups (3-yr: 27% vs 30%, 5-yr: 4% vs 8%). These results suggest that adjuvant treatment postponed the incidence of recurrence during the first two years after treatment but it did not increase the cure rate [45]. Presently, the FAM regimen as used in this study is regarded suboptimal. A major problem faced in adjuvant therapy is the delay of treatment because the morbidity of the pancreatectoduodenectomy often prevents early start of postoperative treatment. This also affected the accrual in the adjuvant studies. Neoadjuvant treatment can overcome this problem. In addition, neoadjuvant treatment may reduce the proportion of cancers with positive resection margins and possibly prevent peritoneal tumor cell implantation due to the manipulation during surgery. Indeed, phase II studies of neoadjuvant chemoradiation suggest that a greater proportion of patients will receive potentially beneficial adjuvant treatment without delay of subsequent surgery [46]. However, despite improved local control there was no improvement of survival because the majority of patients developed distant metastatic disease, predominantly in the liver [47]. As mentioned before, there is a clear need for more active systemic treatments.

**New developments in pancreatic cancer**

Until now, despite intensive chemotherapy, radiation therapy and extensive surgery only modest improvement in the course of pancreatic cancer has been achieved. Furthermore, effective treatment for most patients with pancreatic cancer is not to be expected in the short run. Nevertheless, new treatment modalities of potential use in pancreatic cancer are in development. Pancreatic cancer has demonstrated to possess antigenic targets for immune reactivity, including oncogene products (K-ras, Her-2-neu), mucin products and oncofetal proteins (CEA). Immunotherapy, with the use of genetically modified tumor cell vaccines producing immunostimulatory cytokines, or the use of transfected dendritic cells expressing tumor antigens, is under research and may become useful, especially in patients with minimal disease [48]. Intratumoral injections with ONYX-015, an E1B-deleted group C adenovirus, which selectively replicates in, and, lyases P53-deficient tumor cells in vitro, showed to be safe and suggested to have some anti-tumor activity in a phase I study [49]. Angiogenesis inhibitors are another class of drug therapy under research and may be of use in the treatment of pancreatic cancer. Also, clinical studies with matrix metalloproteinases are currently under way [50].

**Biliary cancer**

Adenocarcinoma of the biliary tract is a rare tumor in which surgery offers the only hope for cure. After potentially curative surgery, the five-year survival rates have been reported to range from 0%-39% [51]. Except for the fact that biliary cancer is a rare tumor, a major problem in investigating the role of chemotherapy in this malignancy is the fact that the lesions are difficult to measure and often an endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography is required to demonstrate intraductal lesions [52]. Therefore, only a few chemotherapy trials have been performed in advanced biliary cancer including small numbers of patients. The results of these trials were disappointing. Most experience exists with
5-FU with a response rate of only 14% [53]. A recent phase II study of 5-FU continuous infusion and recombinant interferon alpha-2b reported a partial response in 11 of 32 patients (34%) and a median survival time of one year [52]. Although promising, confirmation in other trials is needed. With respect to newer agents, paclitaxel was found not active [54]. Reports from docetaxel and CPT-11 are awaited. Overall, it can be concluded that there is a strong need for clinical trials evaluating new treatment strategies containing sufficient patient numbers.

Conclusion

Although pancreaticobiliary cancer is an aggressive disease with a poor prognosis chemotherapy treatment, both in advanced and operable disease, deserves to be an option offered to patients suffering from this disease. Studies do show that a significant proportion of patients derives benefit from this treatment. Furthermore, palliative care remains a very important issue, even more when the decision is made to start treatment. Improvement of outcome is especially awaited from better neoadjuvant and adjuvant approaches. New treatment modalities such as like gene therapy, immunotherapy and antiangiogenic therapy will hopefully become part of our armamentarium in these diseases.

References


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