Review

Pancreaticobiliary cancer: The future aspects of medical oncology

J.M.G.H. van Riel, G. Giaccone & H.M. Pinedo
Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands

Summary

Pancreatic cancer is one of the most common and most lethal cancers in the Western world with a median survival of approximately 3 months. Thus far, the results of anti-cancer treatment have been dismal, with a median survival of only 20 months in resectable pancreatic cancer, and 6 months in advanced disease. Although combined chemoradiation results in improved local control, it has only a modest impact on survival due to the development of distal metastases. In this review we will discuss the progress made in the treatment of pancreatic cancer over the past few years and discuss future therapies such as: immunoradiotherapy, matrix metalloproteinase inhibitors, anti-angiogenesis therapies, gene therapy, immunotherapy, ONYX-015, and farnesylation inhibitors.

Key words: pancreatic cancer, chemoradiation, gemcitabine, immunoradiotherapy, matrix metalloproteinase inhibitors, anti-angiogenesis therapies, gene therapy, immunotherapy, ONYX-015, farnesylation inhibitors

What is accomplished thus far?

Resectable pancreatic cancer

Presently radical surgery is considered the sole treatment for pancreatic cancer with curative intent. Unfortunately surgery is feasible in only 10%-20% of patients presenting with the disease and, even when combined with chemotherapy and/or radiation therapy, results remain dismal with a 5-year survival of 20% and a median survival time of less than 20 months [1-3]. Studies showed that especially patients with positive resection margins had a poor outcome with a prognosis essentially the same as nonresectable disease [3]. A GITSG study showed that adjuvant chemoradiation (5-FU combined with radiation) resulted in a survival at 10 year of 19% versus 0% in the control patients who received supportive care alone [4, 5]. However, some doubt was cast on these results by the negative outcome of a British study which compared the same regimen with surgery alone and failed to establish improved survival for patients receiving adjuvant therapy [4]. Hopefully trials performed by the EORTC (adjuvant 5-FU-based chemoradiation versus surgery alone) and the EPSAC (surgery alone versus adjuvant 5-FU-based chemoradiation with or without continued 5-FU and leucovorin versus 5-FU and leucovorin alone) will clarify some of these uncertainties [4, 6]. A major problem in adjuvant treatment is the morbidity resulting from pancreaticoduodenectomy, which also affected patient accrual in many studies and might have induced an inclusion bias with patients with good performance status more likely to be entered on study. Neoadjuvant therapy may overcome this problem. Other possible advantages of neoadjuvant therapy are: 1. The greater efficacy of radiation therapy on well-oxygenated cells which have not been devascularized by surgery. 2. The potential prevention of peritoneal tumor cell implantation by manipulation during surgery. 3. Inadequacy of surgery alone for local tumor control. 4. Restaging at the end of chemotherapy offers the possibility to exclude patients with disseminated disease for laparotomy thereby sparing associated morbidity and risk of treatment related mortality [1]. Recent phase II studies do suggest that a greater proportion of patients will receive potentially beneficial adjuvant therapy without a delay in operation because of treatment related toxicity when chemoradiation is administered prior pancreaticoduodenectomy [1]. Furthermore, loco-regional tumor recurrence was seen in only 10% to 20% of patients who completed treatment. However, survival duration remained limited because of the development of distant metastases (60%-79% of patients) mainly to the liver [1, 7, 8].

Locally advanced pancreatic cancer

At diagnosis approximately 40% of patients have locally advanced inoperable disease with involvement of regional lymph nodes or adjacent tissues [9]. Early studies have shown that although combined chemoradiation improved local control there was no major impact from both radiation therapy and / or 5-FU-based chemotherapy on survival [10-12]. A more recent phase II study showed that combined chemoradiation (5-FU, streptozocin, cisplatin combined with 50 Gy followed by 12 months maintenace 5-FU plus leucovorin) is effective in achieving durable local control. Of interest, none of the responders (43%) progressed within the radiation field. Moreover downstaging of locally advanced disease occurred, and patients who were able to undergo subsequent resection showed prolonged survival [13, 14]. Progression during and after treatment occurred mainly at distant sites.

Advanced (metastatic) pancreatic cancer

40% of patients present with metastatic disease [9]. In these patients effective palliation, with management of jaundice, duodenal outlet obstruction and pain, remains the objective [15]. For many years 5-FU and 5-FU based combination regimens were the cornerstone of chemotherapeutic treatment. Treatment results were disappointing. However,
In this perspective the use of radiolabeled monoclonal antibodies in combination with gemcitabine as the occurrence of distant metastases, the major reason for results of gemcitabine in advanced disease do suggest that may be required in the neoadjuvant setting. Furthermore, the combination regimen, and much lower doses of gemcitabine fistulae might complicate surgery after this particular properties of gemcitabine like gastric or duodenal ulceration, complications related to the potent radiosensitizing the treatment of resectable pancreatic cancer. However, new therapeutic approaches aiming at tumor specificity and reduced toxicity. In the following section we will highlight some treatment options for future consideration in the treatment of pancreatic cancer.

New directions in the treatment of pancreatic cancer

Despite local control and downstaging by combined treatment no important survival benefit is being obtained. The major reason for treatment failure is distant disease unresponsive to systemic therapy. Therefore, in order to improve survival in pancreatic cancer there is a need for more effective systemic therapies. Until recently conventional chemotherapy was the mainstay of systemic anticancer treatment. Most conventional chemotherapeutic agents are characterized by their lack of specificity for tumor cells, being most effective against rapidly proliferating (malignant) tissues. However, current progress in understanding cancer biology, has resulted in new therapeutic approaches targeting tumor vasculature and reduced toxicity. In the following section we will highlight some treatment options for future consideration in the treatment of pancreatic cancer.

Combined chemoradiation treatment: gemcitabine and radiolabeled monoclonal antibodies

Besides the efficacy of gemcitabine in advanced pancreatic cancer this new antimetabolite is also a potent radiosensitizing drug [19]. Combined chemoradiation using gemcitabine is a logical consequence of these observations. Phase I studies in locally advanced disease demonstrated that weekly or biweekly gemcitabine combined with radiation is feasible with acceptable toxicity [20-23]. Based on these results we have initiated a phase II study in which patients with locally advanced pancreatic cancer are treated with gemcitabine 300 mg/m² combined with 800 cGy external beam radiation delivered on day 1, 8 and 15. When possible after 2 weeks rest treatment will be continued with gemcitabine 1000 mg/m² on day 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity. The ultimate goal will be to implement this treatment regimen in the treatment of resectable pancreatic cancer. However, new complications related to the potent radiosensitizing properties of gemcitabine like gastric or duodenal ulceration, fibrosis of the stomach and surrounding tissues and enteral fistulae might complicate surgery after this particular combination regimen, and much lower doses of gemcitabine may be required in the neoadjuvant setting. Furthermore, the results of gemcitabine in advanced disease do suggest that the occurrence of distant metastases, the major reason for treatment failure, will not be overcome with this approach. In this perspective the use of radiolabeled monoclonal antibodies in combination with gemcitabine as radiosensitizer seems more attractive because of the systemic character of this approach. Possible antigenic targets could be K-ras, mucine products and oncofetal antigens (CEA) [24].

The Matrix Metalloproteinase inhibitors in pancreatic cancer

The process of invasion and metastasis of cancer cells requires penetration of surrounding tissue, blood vessels and lymphatic vessels. It has been shown that Matrix Metalloproteinases (MMPs) and plasminogen activators play an important role these processes. MMPs are a family of enzymes responsible for the degradation of the extracellular matrix. The MMPs are classified in four groups according to substrate specificity of the hydrolyzing enzymes: 1. the collagenases, which have fibrillar collagen as substrate, 2. the gelatinases for nonfibrillar collagen; 3. the stromelysins for proteoglycans and glycoproteins, and 4. the metalloelastases which hydrolyze elastin [25]. The activity of the MMPs is balanced by local metalloproteinase inhibitors. Over the past 10 years a number of these metalloproteinase inhibitors (MMPIs) have been developed for clinical use. Essentially MMPIs have shown not to affect tumor cells but in vivo models have shown tumor growth delay and reduction in the number of metastases. Therefore, clinical endpoints such as objective tumor response are unsuitable for evaluation of this class of drugs. In order to overcome these difficulties overall survival and time to progression have become major endpoints in phase III studies and surrogate endpoints such as tumor marker levels have been introduced. At the moment BB-2516 and BAY 12-9566 have been studied most extensively in patients with pancreatic cancer [26]. A phase II study of BB-2516 (marimastat) demonstrated a significant decay in the rise of CA 19.9 [27]. Furthermore, comparison of survival of patients with advanced pancreatic cancer treated with marimastat with historical controls receiving only supportive care, suggests that the drug might have a beneficial effect on survival [25]. However, the rate of rise in tumor markers and comparisons with historical controls need to be interpreted carefully. Therefore, results of phase III studies comparing marimastat to gemcitabine, marimastat plus gemcitabine to gemcitabine alone which completed accrual, are to be awaited. Also, the ongoing study comparing BAY 12-9566 to gemcitabine will hopefully bring some additional information.

Angiogenesis inhibitors

A reason for the poor prognosis in pancreatic cancer is the development of early metastases regardless the primary tumor growth [28]. Angiogenesis, the development of new blood vessels from pre-existing blood vessels, is essential for both tumor growth and development of metastases. Solid tumors do not grow larger than 1 mm in the absence of neovascularisation [29]. While normal endothelial cells divide rarely, tumor endothelial cells divide at a rate which is at least 50-fold. Angiogenesis is controlled by pro-angiogenic and anti-angiogenic factors [30]. Among the pro-angiogenic factors vascular endothelial growth factor (VEGF) is the most potent and specific growth factor [31]. This growth factor is upregulated in many tumors. Since pancreatic cancer metastasizes early regardless the size of...
the primary tumor it was expected that VEGF was upregulated in this disease. Indeed, VEGF was overexpressed in 64% of the tumors and the presence of VEGF was associated with an increased blood vessel number, larger tumor size, and enhanced local spread but not with a reduction in patient survival time [28]. Recent data suggests that VEGF upregulation is due to mutations of the K-ras oncogene which occur in 75-90% of pancreatic adenocarcinomas. Similar to MMPs, angiogenesis inhibitors are not cytotoxic, but aim at a reduction of tumor cell proliferation, invasion and metastasis. For this reason they have also become a novel therapeutic class of anticancer agents for particular use in early disease. At this moment angiogenesis inhibitors, among which monoclonal antibodies to VEGF and VEGF receptor blockers, are undergoing extensive early clinical study [32]. No study has been initiated in pancreatic cancer yet.

**Ras farnesylation inhibitors**

Alterations in the cellular genome affecting the functions of genes controlling cell growth and differentiation are considered the main cause of cancer. In pancreatic cancer a number of characteristic genetic abnormalities have been identified. In about 90% of the pancreatic adenocarcinomas a mutated K-ras gene has been found, most mutations located in codon 12. Ras genes are a family of proto-oncogenes. Their products are transmembrane proteins that transduce an external stimulus (i.e. growth factor or factors involved in cellular differentiation) which eventually results in cellular division and proliferation. The mutated ras proteins have lost their ability to be inactivated leading to unregulated cellular growth or differentiation [33, 34]. Farnesylation, the attachment of a farnesyl group to the ras protein, allows insertion of the molecule into the plasma membrane and is necessary for ras activity. Farnesylation inhibitors have attracted interest as ras inhibitors and antineoplastic drugs and might be of interest in future treatment of pancreatic cancer.

**Gene therapy and immunotherapy**

Gene therapy involves a number of therapeutic approaches that use recombinant DNA technology. Gene based therapies for cancer include strategies that involve augmentation of chemotherapeutic and immunotherapeutic approaches. Transduction of tumor cells with a gene encoding an enzyme which converts a nontoxic prodrug to a cytotoxic drug is a strategy used in virally directed enzyme prodrug therapy (VDEPT). With the use of a replication-defective recombinant retroviral vector a foreign gene encoding an enzyme capable of converting a harmless prodrug into a cytotoxic compound is introduced. The retroviral vector is capable of infecting normal cells as well as malignant cells. However, the gene is linked to a transcriptional control element (promoter) selective for a particular tumor type so that significant transcription of the gene is activated only in tumor cells [35]. An example of this approach in pancreatic cancer is the transfection of tumor cells with the gene encoding the enzyme herpes simplex virus thymidine kinase (HSVTK) which metabolizes the prodrug gancyclovir to a toxic triphosphate that interrupts DNA synthesis in proliferating cells. In animal studies human pancreatic carcinoma showed complete regression after intratumoral injection of the HSVTK gene linked to the tissue specific CEA promoter and subsequent treatment with gancyclovir [36]. However, intratumoral injection is far from ideal and there is a need for more efficient methods of gene transfer.

Another gene therapeutic approach is the use of recombinant DNA constructs expressing cytokines and lymphokines in order to enhance the immune response against cancer cells. In tumor bearing animals vaccination with pancreatic tumor cells genetically engineered to secrete interleukine-2 and gamma-interferon cytokines resulted in inhibition of tumor growth [37]. Dendritic cells are relatively recently discovered cells that play an important role in establishing an immune response. Their function as professional antigen presenting cells makes them a tool for cancer immunotherapy. An interesting approach to enhance the immune response against the tumor is the vaccination of ex vivo generated autologous dendritic cells loaded with tumor antigen [38]. Among the tumor antigens of interest in pancreatic cancer are mutant-ras and MUC-1. In pancreatic cancer specific T-cell responses against mutant-ras were found after vaccination with mutant-ras peptide pulsed dendritic cells [39]. And, by means of retroviral transfection, genetically modification of dendritic cells to express the MUC-1 protein in order to stimulate the immune response is possible [40]. These approaches and their possible use in pancreatic cancer need further investigation.

**ONYX-015**

p53 is a tumor suppression gene, which mediates cell-cycle arrest and/or apoptosis in response to DNA-damage or foreign DNA synthesis (for example, during virus replication). Inactivation of p53 results in the loss of two major controls of cell growth: the regulation of proliferation and the induction of cell death [41]. Loss of p53 function may lead to resistance to chemotherapy and/or decreased survival. In order for DNA viruses to replicate efficiently in human cancer cells p53 function has to be blocked. The 55 kDa protein form the E1B-region of adenoviruses is shown to be essential for the binding and inactivation of p53 and thus allowing efficient virus replication. ONYX-015 is an E1B-deleted group C adenovirus. Because of the deletion in the E1B 55-kDa gene ONYX-015 selectively replicates in and lyses p53-deficient tumor cells [42]. Preclinical research demonstrated both antitumoral efficacy and selectivity with human tumor cells lacking normal p53 function being highly sensitive to ONYX-015 mediated cytopathic effects and, normal human cells being resistant [41]. Since in pancreatic cancer p53 is inactivated in 50% to 75% of patients ONYX-015 might be of interest in this disease [43, 44]. Recently preliminary results of a phase I trial of intratumoral injection of ONYX-015 in unresectable carcinoma of the exocrine pancreas were presented. Of the sixteen patients treated 14 were evaluable for response. 4 had minor regression, 7 stable disease, and 3 progressive disease. The authors concluded that these data suggest some anti-tumoral activity and a phase II study is planned [45].

**Conclusion**

With traditional anticancer therapy only little progress is
made in the treatment of pancreatic cancer and survival remains poor. However, completely new therapeutic strategies are under development. Although, much work has to be done before implementation in daily practice will be a fact, we hopefully expect that they result in better outcome in patients with pancreatic cancer.

References


28. Folkman J. What is the evidence that tumors are angiogenesis dependent. Journal of the National Cancer Institute 1990;90:8-6.


