REVIEW ARTICLE

Drugs 2000 May; 59 (5): 1071-1089
0012-6667/00/0005-1071/$25.00/0

Pancreatic Cancer

A Review of Emerging Therapies

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Abstract

The incidence of adenocarcinoma of the pancreas has risen steadily over the past 4 decades. Since pancreatic cancer is diagnosed at an advanced stage, and because of the lack of effective therapies, the prognosis of such patients is extremely poor. Despite advances in our understanding of the molecular biology of pancreatic cancer, the systemic treatment of this disease remains unsatisfactory. Conventional chemotherapy has not produced dramatic improvements in response rates or patient survival. New treatment strategies are clearly needed. This paper reviews emerging therapies for pancreatic carcinoma. A more profound understanding of the molecular biology of cell growth and proliferation, as well as of neoplastic cell transformation, has led to advances in several areas, including the use of somatostatin analogues and antiandrogens as adjuvant therapy; inhibition of tumour growth and metastasis by inhibitors of matrix metalloproteinases and angiogenesis, and by small molecules such as retinoids, which interfere with

progression through the cell cycle; immunotherapy with monoclonal antibodies; disruption of intracellular signal transduction with farnesyltransferase inhibitors; and finally gene therapy with specifically designed vaccines.

1. Pancreatic Cancer

The incidence of adenocarcinoma of the pancreas has risen steadily over the past 4 decades. It currently stands at approximately 29 000 new cases per year in North America,[1] making it the second most common gastrointestinal malignancy and the fifth leading cause of adult deaths from cancer.[2] The disease is characterised by its aggressive nature. The diagnosis of pancreatic cancer is usually established at an advanced stage, and a lack of effective therapies leads to an extremely poor prognosis. A meta-analysis of 144 reported series including approximately 37 000 patients found the median survival time to be 3 months.[3] According to these findings, 65% of patients with pancreatic cancer die within 6 months from the time of diagnosis, and about 90% within 1 year. Surgical resection, if performed early enough, is currently the only effective form of curative therapy.[4] However, fewer than 15% of patients with pancreatic cancer are potential candidates for a curative resection[5] because of spread of the cancer to adjacent tissues or beyond.[6] Only 1 to 4% of patients with adenocarcinoma of the pancreas will survive 5 years after diagnosis.[7,8] Thus the incidence rates are virtually identical to mortality rates.

Approximately half of all patients with pancreatic cancer have metastatic disease at the time of diagnosis,[9,10] and most of the rest have locally advanced, unresectable disease.[11,12] Metastatic pancreatic cancer is one of the most chemotherapy-resistant tumours, as evidenced by the fact that pancreatic cancer has the lowest 5-year survival rate (3%) of any cancer listed in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute.[13]

Computed tomography (CT) and magnetic resonance imaging (MRI) have made it easier to determine the diagnosis and to define the stage of the disease. CT guided needle biopsies and laparoscopy have resulted in fewer unnecessary laparotomies, while biliary stenting can reduce the need for an invasive operative procedure in patients with advanced tumours. Unfortunately, these advances have not resulted in disease detection at an earlier stage.[14]

Reports of 5-year survival among patients managed with nonsurgical therapies remain anecdotal. Thus, of 150 patients who have survived for more than 10 years after their diagnosis of pancreatic cancer, only 12 have been cured by nonsurgical therapies.[3] Clearly, more effective therapies need to be developed.

1.1 Risk Factors

A number of factors that may contribute to the pathogenesis of pancreatic cancer have recently been identified. These have been classified as environmental factors, pathological factors (e.g. chronic pancreatitis), genetic factors (e.g. familial pancreatic cancer) and occupational exposure.[15,16]

Currently, cigarette smoking is the most firmly established risk factor associated with pancreatic cancer. Pancreatic malignancies can be induced in animals through long term administration of tobacco-specific N-nitrosamines or by parenteral administration of other N-nitroso compounds.[17-19] Induction of pancreatic cancer in these experimental models can be influenced by additional factors, including changes in bile acid composition, cholecystokinin levels, diet, and pancreatic duct obstruction.[20-23]

Clinically, numerous case-control and cohort studies have reported an increased risk of pancreatic cancer for smokers in both the US and Europe, and current estimates suggest that approximately 30% of pancreatic cancer cases may be attributed to cigarette smoking.[24,25]

1.2 Pathology

Most malignant pancreatic tumours (95%) are believed to arise from the exocrine portion of the gland and have light microscopic features consis-

tent with those of adenocarcinomas. Much more infrequent are tumours that arise from acinar cells or islet cells. Primary non-epithelial tumours of the pancreas (e.g. lymphomas or sarcomas) are exceedingly rare.

1.3 Natural History

Adenocarcinoma of the pancreas metastasises to regional lymph nodes at an early stage of the disease, and subclinical liver metastases are present in the majority of patients at the time of diagnosis, even though findings from imaging studies may be otherwise normal. Patients who undergo surgical resection for localised non-metastatic cancer of the head of the pancreas have a long term survival rate of approximately 20% and a median survival of 15 to 19 months. However, disease recurrence following a potentially curative Whipple resection is the norm.

Local recurrence occurs in up to 85% of patients who undergo surgery alone, and local-regional tumour control may be improved by combined modality therapy involving both chemoradiation and surgery. Liver metastases then become the dominant form of tumour recurrence and occur in 50 to 70% of patients after potentially curative combined modality treatment.

Patients with locally advanced, non-metastatic disease have a median survival of 6 to 10 months, whereas those with metastatic disease have a short survival (3 to 6 months), the length of which depends on the extent of disease and performance status.

Because of the prognosis and the patterns of treatment failure associated with adenocarcinoma of the pancreas, any proposed treatment must not be worse than the disease. The low cure rate and modest median survival following a Whipple's resection mandate that treatment-related morbidity must be low and treatment-related death be rare. A recent report of the experience from Johns Hopkins University, Baltimore, Maryland, USA, demonstrates that this can be achieved by careful selection of patients who undergo therapy.[26] In addition, however, the development of innovative treatment strategies directed at the known sites of tumour recurrence should be focused on improvements in patient survival and quality of life.

2. Historical Overview of Pancreatic Cancer Therapies

2.1 Phase II Trials

Single agent phase II trials in patients with advanced pancreatic cancer reported large variations in response rates.[27,28] In evaluating these studies, it is important to realise that clinical trial methodology and the criteria for judging objective response have changed with time.[27] Phase II trials in the 1970s often included patients with a variety of different tumours in a single trial, and therefore the published response rates were frequently based on a small number of patients with a particular cancer. As a result, these studies were difficult to interpret from a statistical point of view.

Prior to 1985, trials relied primarily on an estimation of tumour size by physical examination and responses were defined as shrinkage of a palpable abdominal mass by 50% or more, or a reduction in the palpable liver span by 30% or more.[28] The inherent inaccuracy of these techniques, intra-observer and inter-observer variability, and the influence of confounding factors on the size of the measured lesions all contributed to the initial reports of high response rates for drugs such as fluorouracil (5-FU), chlorambucil and mitomycin, as well as the failure to confirm these promising response rates in subsequent trials, especially when CT scans were used to determine tumour response.[27]

2.2 Phase III Trials

Two kinds of comparative studies have been carried out in patients with advanced pancreatic cancer: those that compared active treatment with best supportive care (to determine whether chemotherapy made any difference in the outcome of these patients); and those that compared multi-agent regimens with single agent chemotherapy (to determine whether combinations of drugs with distinct mechanisms of action could improve outcome com-

pared with that achieved by single agents).[27] Of the three trials that compared active treatment with best supportive care, two demonstrated no significant difference,[29,30] and the third suggested a substantial survival advantage in favour of a 5-drug regimen.[31] However, subsequent trials of the regimen failed to duplicate the promising results of the original study.[32]

Despite a number of potentially interesting preclinical findings and promising phase II studies, virtually no progress has been made in the chemotherapy for advanced pancreatic cancer during the past 30 years.

2.3 Current Approach to Single Agent Chemotherapy

The thymidylate synthase inhibitor fluorouracil remains the most extensively evaluated chemotherapeutic agent for pancreatic cancer.[33-35] Despite numerous trials, however, its efficacy remains questionable.

Between 1991 and 1994, 25 investigational new drugs were evaluated in phase II trials for the treatment of pancreatic cancer. The median response rate in these trials was 0% (range 0 to 14%) and the median survival was 3 months.[28] Inactive drugs that have undergone evaluation over the past 5 years include iproplatin,[36] trimetrexate,[37] edatrexate,[38] fazarabine,[39] diaziquone,[40] mitoguazone,[40] and amonafide.[41] One trial conducted during this period focused on gemcitabine (2′,2′-difluoro-2′-deoxycytidine).[42]

Gemcitabine is a deoxycytidine analogue with structural similarities to cytarabine. As a prodrug, gemcitabine must be phosphorylated to its active metabolites, gemcitabine diphosphate and gemcitabine triphosphate. In both preclinical and clinical testing, gemcitabine demonstrated greater activity against solid tumours than did cytarabine. These observations have been explained by the following properties of gemcitabine: (i) it is 3 to 4 times more lipophilic than cytarabine, resulting in greater membrane permeability and cellular uptake; (ii) it has higher affinity for deoxycytidine kinase; and (iii) the intracellular retention of gemcitabine triphosphate, an active metabolite, is prolonged.[43]

Following a phase I study,[44] gemcitabine was evaluated in a multicentre trial of 44 patients with advanced pancreatic cancer.[45] Although the objective response rate to this drug was only 11% and median survival was 5.6 months, a number of potentially important observations were made in this trial. The 1-year survival rate was a remarkably high 23%, and the responses observed appeared to be somewhat prolonged, i.e. from 4 to more than 20 months. However, perhaps the most unexpected outcome of this study was the impact of gemcitabine on tumour-related symptoms.

160 patients with newly diagnosed, unresectable pancreatic cancer were recruited in a phase III trial.[46] A total of 126 patients completed a period during which pain was stabilised and then they were randomised to treatment with gemcitabine or fluorouracil. 15 patients (23.8%) treated with gemcitabine achieved a clinically beneficial response compared with only 3 patients (4.8%) treated with fluorouracil ($p = 0.002$). The median duration of the clinically beneficial response for gemcitabine-treated patients was 18 weeks compared with 13 weeks for the fluorouracil-treated patients. Gemcitabine also proved superior to fluorouracil in terms of the trial's secondary end-points. Median survival for gemcitabine-treated patients was 5.6 months compared with 4.4 months for fluorouracil-treated patients. In addition, the probability of survival at 1 year was 18% in the gemcitabine group, significantly greater than the 2% in the fluorouracil group. Few objective responses, however, were observed in either treatment arm.

A subsequent phase II study enrolled 63 patients with pancreatic cancer that had progressed despite treatment with fluorouracil.[47] To be eligible for the trial, patients had to have a significant degree of tumour-related symptoms. In this study, 17 patients (27%) experienced a clinically beneficial response to gemcitabine, the median duration of which was 14 weeks. Median survival of all patients treated in this trial was 3.8 months. Objective responses were

seen in 6 (10.5%) of the 57 patients with measurable disease.

While these results could suggest that gemcitabine should become the accepted first-line therapy for patients with advanced pancreatic adenocarcinoma, the median survival for patients with metastatic disease was still less than 6 months, with few patients achieving long term disease stabilisation. Furthermore, some of the effects attributed to chemotherapy may not be substantially different from what can be achieved with aggressive supportive care alone. In fact the use of clinical benefit response as a valid means to determine the efficacy of gemcitabine has itself been questioned.[48] Thus 85% did not survive 7 months, and 8 patients had extension to regional organs or lymph nodes without distant metastases.

The quality of life one seeks to evaluate by defining net patient benefit must take into account the duration of remaining survival available to the patient. Gelber[48] has suggested that performing treatment comparisons based on the amount of time patients spend in clinical health states characterised by relatively good quality of life might be a better indicator of net patient benefit than defining a percentage of patients who achieve some criterion of response. The fact that treatments which produce higher response rates do not always yield better survival also argues against putting too much emphasis in estimating response rates as a guide to net benefit.

17 patients had a clinically beneficial response in the phase II study, and the investigators claimed that the treatment was generally well tolerated.[47] However, although the toxicities were reported as moderate, more patients had some noticeable adverse experiences than achieved a clinical benefit response. The evidence for substantial benefit for gemcitabine is not overwhelming, and additional studies are required to more fully define its role in the treatment of pancreatic cancer.

Preclinical studies have also shown enhanced radiosensitivity of gemcitabine-treated pancreatic cell lines,[49] and several combination therapies with gemcitabine are in phase I and II trials. The initial reports of gemcitabine as a radiosensitiser have been notable for marked toxicity at relatively low dose levels. Hoffman et al.[50] treated patients with localised, resectable pancreatic cancer with combined gemcitabine and radiation therapy before resection. Eight patients required hospitalisation (5 for cholangitis, 1 for pulmonary embolus, 1 for liver abscess, and 1 for gastrointestinal haemorrhage from a perforated gastric ulcer). Wolff et al.[51] are conducting an ongoing phase I study of gemcitabine and radiotherapy in patients with locally advanced pancreatic cancer. Gemcitabine was administered weekly at a starting dose of 400 mg/m^2 with 300 cGy/day radiation. At 400 mg/m^2 gemcitabine, 4 of 9 patients required hospitalisation for treatment–related toxicity. At 500 mg/m^2 gemcitabine, 3 of 3 patients required hospitalisation for nausea, vomiting and dehydration. The appropriate phase II dose has not been established.

In summary, despite a rather meagre effect on survival, gemcitabine remains the only chemotherapeutic agent at this time that can be considered as first-line therapy for this disease.

3. Emerging Approaches to Pancreatic Cancer

Despite advances in our understanding of the molecular biology of pancreatic cancer, the systemic treatment of metastatic disease remains unsatisfactory. Systemic chemotherapy and the administration of biologically active molecules such as tumour necrosis factor or interferons have not resulted in significant improvements in response rates or patient survival.[52,53]

A number of more general areas of investigation may yield more promising results. One of these involves interruption or modulation of growth factors and signal transduction pathways. One example is the successful treatment of carcinoma of the breast that has been achieved by endocrine manipulation. The presence of estrogen receptors on neoplastic breast tissue is correlated with response to ovarian ablation and/or antiestrogen treatment. A similar approach to the treatment of pancreatic cancer seems justified because of the presence of

estrogen receptors in pancreatic carcinoma[54-57] as well as in normal pancreatic tissue.[58,59] In fact, the use of tamoxifen in 80 patients with ductal adenocarcinoma of pancreas has been reported in a case-control study to increase the median survival time from 3 months to 7 months.[60,61] However, steroid hormones may not be the most important regulator of pancreatic cell proliferation. Other potential influences include insulin-like growth factor (IGF)-1 and the growth inhibitor somatostatin.

3.1 Biological Basis for Somatostatin-Based Therapies

Somatostatin is a tetradecapeptide that elicits a variety of biological processes including inhibition of hormonal secretion and cell proliferation.[62] In some patients, analogue therapy leads to an inhibition of tumour growth.[63-65] However, the use of native somatostatin is limited because of its very short plasma half-life and the need for continuous infusion. The recent development of long-acting somatostatin analogues, such as vapreotide (RC-160) and octreotide (SMS-201995), however, has made clinical trials possible.

These properties of somatostatin form the basis for the treatment of hormone-producing pituitary or gastroenteropancreatic tumours by long-acting analogues of the native hormone.[63] Thus, hormonal suppression is produced in patients with acromegaly or with neuroendocrine tumours such as insulinoma, glucagonoma, gastrinoma, vipoma (diarrhoeogenic tumour) or carcinoid syndrome by somatostatin analogues, resulting in symptomatic relief.[63]

Somatostatin can exert an antiproliferative effect either by indirectly inhibiting angiogenesis or hormone and growth factor release, or by acting directly on neoplastic cells.[62-65] For example, a number of gastrointestinal hormones, including gastrin and cholecystokinin, have trophic effects on pancreatic tissue[66] and can stimulate the growth of pancreatic tumours. Somatostatin suppresses the secretion and action of these peptides, and this may also contribute to its antiproliferative activity.[67,68] In addition, somatostatin and its analogues may act by reducing levels of growth factors such as epidermal growth factor (EGF) and IGF-1, which are thought to be important in neoplastic processes.[69-73] This latter possibility is of considerable interest because both tamoxifen[73] and octreotide[74] have been shown to lower circulating levels of IGF-1, and the combination has recently been reported to lower IGF-1 levels more substantially than either agent alone.[75] This observation raises the possibility of therapeutic synergy if the two agents were used together, a suggestion which is supported by a report that tamoxifen and octreotide were effective treatment for human pancreatic cancers growing in nude mice.[76] However, appealing as this suggestion is, Klijn et al.[77] measured insulin, IGF-1 and EGF levels in a clinical study of the use of octreotide for pancreatic cancer. Long term treatment with octreotide had no effect on EGF levels, and although these investigators observed early significant decreases in insulin and IGF-l, the levels of both growth factors had returned to pretreatment values by 5 days and 4 weeks, respectively. This may have been due to the down-regulation of the receptors responsible for inhibiting the release of these trophic factors. This study does not support suppression of trophic peptides as an important mechanism by which somatostatin inhibits pancreatic cancer, but it does not eliminate the possibility that these hormones may influence pancreatic tumour growth.

The direct actions of somatostatin are mediated by specific receptor,[62,63,78-88] and the antiproliferative action of somatostatin and its analogues on pancreatic cancer, in particular, has been demonstrated both *in vitro* and *in vivo*.[65,89] This being said, though, the inhibition of tumour growth by somatostatin and its analogues is rather complex and many gaps remain in our knowledge.[78,82-86,88,90-93]

Only a few studies have so far addressed the potential benefit of combined treatment with octreotide and various chemotherapeutic agents. Lamberts et al.[94] combined octreotide with vincristine, methotrexate, fluorouracil or suramin sodium and found an additive interaction.

More recently, Weckbecker et al.[95] demonstrated the inhibitory effect of octreotide in combination with the chemotherapeutic agents paclitaxel, fluorouracil, doxorubicin and mitomycin on the growth of AR42J pancreatic cancer cells *in vitro*. The dose-dependent antiproliferative effects of mitomycin, doxorubicin and paclitaxel were synergistically enhanced by octreotide. Combinations of octreotide and fluorouracil resulted either in additive or, at high concentrations of the chemotherapeutic agent, in synergistic interactions. Similar effects were observed for a cytotoxic analogue of somatostatin containing methotrexate.[96] These experiments suggest a modulatory role for octreotide in combination with widely used anticancer drugs. The additive to synergistic interaction of octreotide with these chemotherapeutic agents in *in vitro* and *in vivo* models warrants clinical studies to explore the potential of such combinations in the treatment of pancreatic cancer.

3.1.1 Clinical Studies of Somatostatin and its Analogues

Preliminary results of somatostatin analogue therapy in patients with cancer other than pancreatic have been encouraging.[97-100] The rationale for the use of somatostatin and its analogues can be briefly summarised as follows. Somatostatin decreases growth of the normal pancreas,[101] and at least one somatostatin analogue, octreotide, inhibits the growth of human pancreatic adenocarcinoma in nude mice.[89] The demonstration of somatostatin receptors in exocrine pancreatic adenocarcinomas[102] and the large body of evidence[76,102-108] demonstrating antiproliferative activity of somatostatin and somatostatin analogues on experimental pancreatic neoplasms *in vitro* and *in vivo* justify clinical studies on the potential therapeutic role of these drugs in pancreatic cancer.

The first clinical study on somatostatin analogue treatment was published by Klijn et al.[109] This group went on to treat 14 patients who had metastatic pancreatic cancer with 3 daily subcutaneous injections of octreotide (100 to 200μg per injection) for an average of 7 weeks and observed no antitumour effect.[77]

Friess et al.[110,111] and Ebert et al.,[112] using octreotide at a low dose level (3×100 to 200 μg/day) and a high dose level (3×2000 μg/day) suggested that the effects of this somatostatin analogue were dose dependent. These observations are in accord with the dependent relationship of somatostatin analogues on the proliferation in breast cancer cell lines.[113] In the Friess high dose study, the median survival increased from 4 to 6 months with symptomatic and clinical improvement. A positive effect on the course of disease was confirmed by a randomised trial of octreotide versus best supportive care[114] based on a low dose (300 to 600 μg/day) therapy given 5 days per week. In this trial a significant advantage in duration of survival and in percentage of stable disease was observed for the octreotide-treated patients although no objective response was reached.

The only objective response reported for somatostatin analogues in pancreatic cancer was observed by Canobbio et al.,[115] who administered lanreotide (BIM-23014) in dosages between 250 and 1000 μg/day to 18 evaluable patients. However, only one partial response was observed at the highest dose level. Huguier et al.,[116] in a randomised prospective study of 86 patients who were given a similar treatment regimen, demonstrated no significant increase in median survival rates using life-table analysis.

Weckbecker et al.[117] has demonstrated potentiation of the anticancer effect of tamoxifen by concomitant infusion of high dose octreotide in the rat DMBA mammary cancer model. To further define a possible beneficial role for combination hormonal therapy with octreotide and tamoxifen, Rosenberg et al.[118] studied the effect of long term administration of these two inhibitory agents on survival of a prospective series of 12 consecutive patients with biopsy-proven ductal adenocarcinoma of the pancreas followed up from 1990 to 1993. Five of these patients had resectable disease, and in the remaining 7 disease was deemed unresectable. Treatment consisted of octreotide 100μg subcutaneously three times daily and tamoxifen 10mg orally twice daily. The major outcome measured was the

median duration of patient survival in months from the time of diagnosis. The outcome of this group of patients was compared with that of a cohort of 68 patients with a biopsy-documented diagnosis of ductal adenocarcinoma of the pancreas treated between 1985 and 1990.

The median survival times of the octreotide/tamoxifen-treated group and the historical cohort were 12 months and 3 months, respectively, and the 1-year actuarial survival was 59% and 16%, respectively. The median survival times of the 5 resected and the 7 unresected patients were, respectively, 20 and 12 months and the 1-year actuarial survival was 80% and 31%. The median survival times of the resected octreotide/tamoxifen-treated group and the resected historical cohort were 20 and 12 months, respectively, and the 1-year actuarial survival was 80% and 44%. The median survival times of the 7 patients in the unresected octreotide/tamoxifen-treated group and the 59 in the unresected historical cohort were 12 and 2.5 months, respectively, and the 1-year actuarial survival was 31% and 11%. Cox's proportional hazards analysis confirmed that treatment and resection both independently predicted a longer survival. The significance of a possible interaction between treatment and resection could not be fully determined because of the small sample size. CT scanning examinations of the 12 patients were performed at intervals of 6 to 8 weeks, and although no objective responses were seen in terms of tumour regression, the data were consistent with a slowing of tumour progression.

The most recent report is the phase II study by Fazeny et al.,[119] which was designed to investigate the efficacy and toxicity of octreotide combined with goserelin in patients with advanced pancreatic cancer. Octreotide was injected subcutaneously in dosages increasing weekly, starting with 50μg twice daily, until the level of maintenance therapy of 500μg three times daily was reached. In addition, 3.8mg goserelin was administered subcutaneously at monthly intervals. A median of 7 cycles (range 1 to 27) were applied. In comparison to the 40% of patients who had no change in their disease while on high dose octreotide, octreotide 500μg three times daily in combination with goserelin resulted in one partial response and no disease progression in 70% of participants. The observations suggest that combining octreotide with a gonadorelin (luteinising hormone-releasing factor) analogue might be of therapeutic benefit in patients with pancreatic cancer and could compensate for the potential advantage of a higher dose of octreotide. Overall, however, the regimen under investigation did not meet the criteria for sufficient antitumour effectiveness. Nevertheless, this study reinforces the concept that pancreatic cancer is in principle responsive to endocrine therapy and, therefore, further investigation of hormonal manipulation seems worth while in the future.

In summary, while it is clear from the numerous studies conducted on experimental neoplasms *in vitro* and *in vivo* that somatostatin analogues inhibit growth of exocrine pancreatic cancers, clinical studies have demonstrated that somatostatin analogue therapy probably does not produce an adequate clinical response in patients with advanced pancreatic cancer.

3.2 Other Hormonal Strategies

Testosterone may also have a positive effect on the growth of pancreatic carcinoma. The concept is supported by the presence of androgen receptors within human pancreatic cancer tissue[120] together with the enzymes aromatase and 5α-reductase, which, respectively, convert testosterone into estradiol or a more active androgen, dihydrotestosterone.[121] Confirmatory evidence for a central role of testosterone came with the demonstration of its growth potentiating action on human pancreatic adenocarcinoma xenografts grown in nude mice, together with the inhibiting action of antiandrogen.[122] To assess whether flutamide, a pure androgen receptor blocking agent, improved survival in patients with pancreatic cancer, a prospective, randomised, double-blind, placebo-controlled trial was conducted.[123] 24 patients received flutamide and 25 received placebo. Analysis of patients at 6 months and 1 year demonstrated 88% and 50% sur-

vival, respectively, in the flutamide group compared with 50% and 5% in the placebo-control group. Median survival for all patients was 8 months in the flutamide group and 4 months in the placebo group. Therefore, this early study supports the concept that testosterone is a growth factor for pancreatic carcinoma and that blockade of androgen receptors offers a potentially new approach to treatment.

3.3 Farnesyltransferase Inhibitors

Beyond conventional chemotherapy, efforts are focusing on systemic therapies based on a rational approach to the biological properties of the pancreatic cancer cell itself. The *RAS* oncogene and the proteins encoded by it have been the subject of considerable research during the past 10 years. RAS proteins are membrane-bound guanosine triphosphate-binding proteins that act as molecular switches in mitogenic signal transduction. Mutations of the *RAS* gene lead to proteins that are permanently in the active state. These mutations occur in approximately 90% of pancreatic cancers.[124]

RAS proteins require a post-translational addition of a 15-carbon farnesyl group to become attached to the cellular membrane. If this farnesyl addition is blocked, the protein cannot attach to the membrane and remains inactive.[125] Farnesyltransferase inhibitors can block the addition of the farnesyl group and prevent membrane attachment of the RAS protein, leaving it inactive. Various farnesyl transferase inhibitors have been synthesised and found to have *in vitro* and *in vivo* activity. Farnesyltransferase inhibitors entered the clinic for phase I testing in 1998, and phase II and III studies are planned in the near future. These agents are generally given continuously by mouth and have minimal toxicity. Pancreatic cancers will be a prime target for this new class of agent because of the high incidence of *RAS* mutation.

3.4 Cell Cycle Inhibitory Factors

Another target for anticancer therapy is the cell cycling machinery itself.[126] The antiproliferative activity of a new retinoid, mofarotene (RO-408757), on 9 pancreatic cancer cell lines has been examined for its effects on various cell cycle-regulating factors, including cyclins D1, E and A, cyclin-dependent kinases (2 and 4), cyclin-dependent kinase inhibitors (p21 and p27) and retinoblastoma protein. Mofarotene showed half-maximal inhibition of cell proliferation at concentrations that produced little cytotoxicity. A marked increase in the fraction of cells in G1 phase of the cell cycle was observed in association with up-regulation of p21/p27 and a shift of retinoblastoma protein into the hypophosphorylated form. Therefore, mofarotene and other similar molecules could represent a new approach to pancreatic cancer therapy.

3.5 Gene Therapy

Novel gene therapy strategies that also target cell cycle progression are under development. One of the more promising approaches is that reported by Joshi et al.[127] and is based on the *p21WAF-1* gene and an adenovirus vector. Dergham et al.[128] have shown a significant survival advantage in patients treated with conventional therapies whose tumours expressed p21WAF-1. The p21WAF-1 protein is an important inhibitor of cell-cycle progression. Preliminary studies showed a significant dose-dependent increase in p21WAF-1 protein expression in pancreatic cancer cell lines infected with a recombinant adenovirus-*p21WAF-1* construct (rAD-p21), with concomitant cell-growth arrest at G0/G1.[129] Use of the rAD-p21 construct also resulted in significant growth inhibition of pancreatic cell lines in tissue culture.[129] The same group has gone on to conduct preclinical trials of rAD-p21 using a model of human pancreatic adenocarcinoma implanted in the pancreas of SCID (severe combined immunodeficiency) mice.[130] Daily intratumoral injection significantly reduced tumour mass when compared with injections of phosphate-buffered saline or adenovirus alone.

However, there are drawbacks to the use of such viral vector constructs, including the low transduction rate and the induction of a severe host immune response caused by high titres of adenoviral vectors.[131] Replication-restricted viruses, such as G207, may offer an alternative to adenovirus- or

retrovirus-based transduction vectors. Replication restriction denotes a viral gene vector that is capable of replication only within a desired cell type, such as cancer cells. G207 is an attenuated and multimutated form of herpes simplex virus (HSV) type 1.[132,133] The specific mutations ensure viral replication specifically in targeted cells, thereby making it ideal for cancer therapy. Lee at al.[131] have recently shown that G207 exhibited a dose-dependent cytotoxicity against three human pancreatic cell lines, AsPC-1, MIAPaCa-2 and BxPC-3. It is also important to note that following cell infection, expression of early viral genes is supported. This opens up the possibility of introducing different genes into cells by inserting such genes into the nonessential region of the HSV early genome, which will present opportunities for more specific gene therapies. Furthermore, in the study by Lee et al., viral growth was supported by each of the cell lines tested.[131] As for *in vivo* application, support for viral production eliminates the need for repeated cell transduction by retrovirus vectors carrying the *HS-tk* gene, for example, a well known 'suicide' gene.[134]

At this point, the host range of replication restriction for G207 has not been defined in humans. Further therapeutic evaluation of this promising viral vector seems warranted.

3.6 Vaccines

Immunotherapy as a potential alternative systemic treatment for adenocarcinoma of the pancreas has recently been reviewed by Yeo.[135] The advantage of this approach over radiation and chemotherapy is that it can act specifically against the tumour, without causing damage to normal tissues. Vaccines are one form of immunotherapy, which can also provide active immunisation that allows amplification of the immune response. In addition, vaccines can generate a memory immune response. Recent advances in the understanding of the mechanisms of immune system activation have revealed that any cellular protein (expressed in virally infected cells or cancer cells, including pancreatic cancer cells) can be recognised by the immune system if those proteins are presented to the immune system in a form that results in activation rather than ignorance or tolerance to that antigen. In addition, T cells rather than B cells are responsible for this recognition.

There are generally two ways in which pancreatic and other tumour cells are currently being genetically modified to more efficiently present their tumour antigens to the immune system, resulting in potent activation of a systemic antitumour immune response. In the first model, tumour cells are genetically modified to express cytokines (proteins normally expressed as paracrine factors by immune cells to orchestrate immune responses) that attract professional antigen presenting cells (APCs) such as macrophages or dendritic cells to the site of the tumour cell. These APCs have the ability to activate both helper and killer T cells. Evidence suggests that the helper T cells can significantly potentiate killer T-cell growth factors. In the second model, tumour cells are genetically modified to express costimulatory surface molecules or cytokines that can directly attract and activate killer T cells, often bypassing the helper T cell arm. Both of the above approaches have been tested in preclinical models.[82,136]

Genetically modified tumour cell vaccines that express various cytokines are already being tested in phase I studies, but for tumours other than pancreatic adenocarcinoma.[137,138] One study evaluated autologous renal tumour cells that had been genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with stage 4 renal cell carcinoma.[137] Immune responses in the form of delayed type hypersensitivity reactions against autologous tumour cells after vaccination were observed in 3 of 3 patients. Interestingly, 1 of the 3 patients demonstrated an associated partial response of pulmonary metastases. These early studies have also revealed several problems that limit the feasibility of autologous tumour vaccines. First, it is technically difficult to isolate and expand *in vitro* autologous tumour cells for vaccine production for most histological tumour types including pancreatic cancers. Second, an au-

tologous vaccine implies that it is individual therapy and therefore not generalisable to all patients with the same cancer. Third, it is very expensive to produce an individual vaccine for each patient.

To overcome these limitations, Jaffee et al.[139] have developed an allogeneic vaccine approach. Allogeneic vaccine cells that have been genetically modified to express GM-CSF should be feasible because GM-CSF attracts the intermediate professional APCs for the purpose of activating helper and killer T cells. Therefore, the tumour cell itself does not have to be major histocompatibility complex compatible with the host's T cells to activate an immune response. Additionally, in malignant melanoma, which is the only human tumour for which many tumour antigens have been identified, it has been shown that the majority of antigens recognised by T cells are shared antigens expressed by over 50% of other patients' tumours. Therefore, it should be possible to vaccinate patients with a histologically similar set of established tumour lines and still activate systemic antitumour immunity. This approach is currently being tested in patients with stage 1, 2 and 3 pancreatic adenocarcinoma at Johns Hopkins Hospital, Baltimore, Maryland, USA.[140]

Other more potent vaccines continue to be developed in preclinical models. These approaches use tumour-associated antigens either in the form of proteins or peptides mixed with defined adjuvants administered systemically. Antigen-based vaccines eliminate the need for the genetic manipulation of tumour cells. This simplifies the vaccine production process and should result in more generalised vaccines. In addition, antigen-based vaccines allow greater control over the amount of antigen formulated in the vaccine, which should translate into improved efficacy. In fact, some of these strategies have been demonstrated in preclinical models to be over 10-fold more potent than the whole cell vaccine approach. Several pancreatic cancer-associated antigens have been identified, including mutated K-ras and p53, reactivated carcinoembryonic antigen (CEA), the altered mucin MUC-1, and overexpressed HER-2/neu. Several of these antigens are currently undergoing phase I testing either mixed with defined antigens or pulsed directly onto autologous dendritic cells (professional APCs) that are isolated from the peripheral blood of each patient, expanded and activated *in vitro*, and then given back by adoptive transfer. Future antigen-based vaccine approaches will undoubtedly use newly identified pancreas-associated antigens that are delivered in recombinant viral vectors that also contain other immune stimulatory genes to further enhance antitumour immunity.

3.7 Monoclonal Antibodies

Another immunotherapy approach to the treatment of pancreatic cancer involves the use of monoclonal antibodies (MAbs). This subject has recently been reviewed extensively by Friess et al.[140]

The MAb edrecolomab (17-1A) is a murine immunoglobulin (Ig)G2a isotype, which was developed by immunising mice with the supernatant of colorectal carcinoma cell line SW1038. This MAb is immunoreactive with a variety of gastrointestinal malignancies and was originally used in clinical trials enrolling patients with colorectal, pancreatic and gastric cancers.[141] Following binding to a 37kDa glycoprotein, edrecolomab initiates antibody-dependent cellular cytotoxicity (ADCC) in the presence of monocytes or macrophages,[142] meaning that binding of the antibody to cancer cells leads to the activation of immune cells, which will destroy antibody-labelled cells. In nude mice, administration of edrecolomab inhibited the growth of human tumour and caused an increase in activated macrophages in the tumour mass.[142] In 4 clinical trials[143-147] involving 100 patients with pancreatic cancer, complete response, partial response and stable disease were reported in 1, 5 and 23 patients, respectively.

BW-494 is a murine IgG1 isotype that recognises a membrane and cytoplasmic 200kDa carbohydrate antigen which is expressed in pancreatic cancer cells.[148] The first clinical trials with BW-494 against pancreatic carcinoma were based on the following characteristics:

- the antibody shows strong binding capacity to well and moderately differentiated human pan-

creatic cancer cells *in vitro* and *in vivo*; immunohistochemical analysis demonstrated a binding sensitivity to more than 90% of pancreatic adenocarcinomas[148-150]

- the antibody mediates ADCC with human mononuclear cells against ^{51}Cr-labelled pancreatic cancer target cells[148]
- *in vitro*, the antibody inhibits specific functions of pancreatic cancer cells, such as endocytosis, superoxide anion generation, and the release of lysosomal enzymes[151,152]
- single injection of ^{131}I-labelled antibody leads to growth suppression of human pancreatic tumours transplanted into nude mice.[153]

Passive immunotherapy using BW-494 was carried out in 145 patients with pancreatic cancer in 2 phase I and 2 phase II trials.[154-158] In 1 of 75 patients a partial response and in 25 of 74 patients stable disease were reported. However, in a controlled, randomised trial of 61 patients after Whipple resection, comparable survival times in patients with and without BW-494 treatment led to the termination of further clinical trials with this antibody.

Clearly, treatment of pancreatic cancer using MAbs is a challenging task that must await the development of new and more potent MAbs, such as chimeric and humanised MAbs which may make the application of higher dosages tolerable and clinically feasible.[159,160] To further improve immunotherapy with MAbs, immune response modifiers such as interleukin-2, colony-stimulating factors, or cytotoxic substances coupled to antibodies will need to be considered.[161-165] Therefore, further clinical studies are necessary to investigate the efficiency of new MAbs and MAb treatment in combination with immunomodulators in patients with pancreatic cancer. One potential new development has been the demonstration of the efficacy of an antibody (trastuzumab) to the HER2/neu oncogene in prolonging survival in metastatic breast cancer in patients whose tumours overexpress HER2/neu. This strategy has been postulated for pancreatic cancer, but it remains to be investigated.[166]

3.8 Matrix Metalloproteinase Inhibitors

Pancreatic cancer is characterised by local invasion of adjacent structures, perineural invasion, early metastases to lymph nodes and liver, and an intense desmoplastic stromal reaction.[167-169] The molecular and cellular processes underlying the epithelial-stromal interactions are of great importance not only for understanding these biological characteristics of the disease, but also because they may represent novel therapeutic targets. This subject has been recently reviewed by Bramhall.[170]

The ability of malignant epithelial cells and induced desmoplastic fibroblasts to degrade adjacent extracellular matrix (ECM) is considered an essential step in the processes of invasion and metastasis.[171-173] The principal component of the basement membrane is type IV collagen, providing the scaffold on which the other major components consisting of laminin and heparan sulfate proteoglycan and the minor components of the ECM are assembled.[174] Loss of basement membrane integrity in breast and colorectal cancers has been shown to be associated with an increased metastatic potential and poor prognosis.[175,176] In pancreatic cancer, there is an absence of basement membrane proteoglycans and a discontinuity or absence of basement membrane type IV collagen.[177,178]

These findings suggest that matrix metalloproteinase (MMP) activity is likely to play an important role in the malignant phenotype of pancreatic cancer.

The MMPs are a family of 17 proteolytic enzymes that share common characteristics. Each degrades at least one component of the ECM, contains a zinc ion and is secreted as a proenzyme, which is activated by cleavage of defined peptide sequences.[179] All MMPs share sequence homologies and are inhibited by specific tissue inhibitors of the metalloproteinases (TIMPs). All of the MMPs are involved in normal remodelling processes such as embryonic development and wound healing, but also play a major role in pathological processes, including tumour invasion and metastasis.[173,180]

Data from a variety of studies (reviewed by Nagakawa et al.[167]) strongly support the hypothesis that

the expression of MMPs 2, 7, 9, 11 and MT-MMP1 (membrane-type MMP1) is important in the phenotype of pancreatic cancer. These studies also suggest that MMP2 expressed in pancreatic cancer by both epithelial and stromal elements may be activated by the MT-MMP1 expressed predominantly by malignant pancreatic epithelial cells. These findings are added to by the possibility that reduced expression of the favoured inhibitor of activated MMP2 (TIMP2) could contribute to the aggressive phenotype, desmoplastic response, and discontinuous basement membrane type TV collagen and proteoglycans seen in pancreatic cancer.

Because of the importance of MMPs in tumour invasion and metastasis, low molecular weight inhibitors of the MMPs have been developed for clinical application. The first synthetic compound to enter clinical trials in cancer patients was a broad spectrum MMP inhibitor (MMPI) batimastat (BB-94), developed by British Biotech Pharmaceuticals (Oxford, UK), which has inhibitory activity against all of the MMPs in the low nanomolar concentrations. The major drawback of batimastat was its low solubility, but further development by British Biotech has led to a related low molecular weight analogue (marimastat; BB-2516) with greater solubility, which was until recently undergoing clinical trials.

Marimastat has now been administered to more than 150 patients with inoperable pancreatic cancer in the UK and US in a phase II clinical trial. Approximately 60% of these patients had stage IV disease, with the remainder having stage II or III disease. The median survival in patients with stage IV disease treated with marimastat was 94 days, and in those with stage II/III disease median survival had not been reached at 3 months. The adverse effects from marimastat tended to be primarily musculoskeletal, and dependent on dose and duration of treatment. Final results of phase III clinical trials are not yet published.

3.9 New Chemotherapy

Taxanes are a new class of anticancer agents believed to exhibit toxicity by disrupting microtubular assembly. Paclitaxel was the first taxane to be widely evaluated in clinical trials. A phase II trial of paclitaxel with granulocyte colony-stimulating factor was undertaken in 35 eligible patients with advanced pancreatic cancer.[181] Stable disease was observed in some patients. There was one response documented. Docetaxel, a semisynthetic taxoid, has also been studied in trials against a wide range of solid tumours.[182] In a phase II trial, 26 patients with advanced untreated pancreatic adenocarcinoma were treated with a 1-hour infusion of docetaxel 100 mg/m^2.[183] Five of 26 evaluable patients (17%) had a partial response with a median response duration of 3 months.

Another new drug under investigation is rubitecan (9-nitrocamptothecin; RFS-2000).[184] This drug appears to be well tolerated and efficacious as first-line therapy for the treatment of advanced pancreatic cancer. It also shows some modest success as second-line therapy in treating patients who have failed gemcitabine therapy.

3.10 Angiogenesis Inhibitors

Angiogenesis, the recruitment of new blood vessels, is critical for the growth of primary tumours above 1 to 2mm in diameter and is an essential component of the metastatic pathway. These vessels provide the principal route by which tumour cells exit the primary tumour site and enter the circulation. For many tumours, the vascular density can provide a prognostic indicator of metastatic potential, with highly vascular primary tumours having a higher incidence of metastasis than poorly vascular tumours. Tumour angiogenesis is regulated by the production of angiogenic stimulators including members of the fibroblast growth factor and vascular endothelial growth factor families. In addition, tumours may activate angiogenic inhibitors such as angiostatin and endostatin which can modulate angiogenesis both at the primary site and at downstream sites of metastasis. The potential use of these and other natural and synthetic angiogenic inhibitors as anticancer drugs is currently under intense investigation and has recently been reviewed by Zetter[185] and Harris.[186] Whether

these and similar drugs will cause tumour regression has not yet been studied in patients. These approaches for advanced disease should be more successful when applied early in an adjuvant situation.

4. Conclusion

It should be apparent from this review of past and current approaches to pancreatic cancer that any progress against this disease will have to come from a combination of advances on two fronts. First, disease detection must be improved. Methods of screening for early disease will need to be developed in concert with the identification of 'at risk' individuals. Second, a multi-modality approach designed to attack different aspects of tumour cell biology will need to be integrated into a treatment regimen that has resectional surgery as its foundation. In this regard, the use of neoadjuvant therapy prior to surgery, and adjuvant therapy following surgery, should play increasingly important roles in the management of pancreatic cancer.

Acknowledgements

L. Rosenberg is a Senior Clinician-Scientist supported by the Fonds de la Recherche en Santé du Québec (FRSQ).

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