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Practical Recommendations for the Management of Adenocarcinoma of the Pancreas

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Contents

Abstract

Pancreatic cancer is widely regarded by medical personnel and the lay public as one of the most dreaded of all diagnoses. Although in selected series of operable patients the chance of long term survival may reach 20%, most patients have unfavourable disease at the time of diagnosis, and for the entire group of newly diagnosed patients, 5-year survival is rare. This grim outlook results from a combination of factors, including an anatomical location which makes early detection by screening tests or by symptoms difficult, a high tendency for spread to regional lymphatics and the liver, a poor profile of sensitivity to chemotherapeutic agents and the poor medical condition of many patients at the time of diagnosis. These factors mean that it is particularly important that at the time of diagnosis these patients are carefully evaluated, and that they and their families are fully aware of the treatment options available to them and the associated potential risks and benefits.

For localised cancers, surgical resection alone offers the potential for long term survival. The addition of postoperative radiation therapy (RT) predictably improves local control but has minimal impact on survival, which is primarily determined by the development of liver metastases. Randomised trial data support the use of combined fluorouracil (5-FU) chemotherapy and RT in patients who have undergone pancreatectomy and have negative margins, although the benefits are modest and the relevant randomised trials enrolled relatively small patient numbers. For patients with marginally resectable tumours, the feasibility has been demonstrated of using chemotherapy plus RT to reduce tumour size before resec-

tion, but it is unclear whether this approach will benefit a significant number of patients. Tumours which are unresectable because of local advancement (involvement of major vessels or regional nodes) can be treated with RT alone or in combination with chemotherapy, but survival past 2 years is uncommon.

Patients with liver metastases have a poor prognosis. As part of a programme of supportive care, some of these patients may receive cytotoxic therapy, the goal of which is to relieve cancer-related symptoms such as pain from the primary tumour or metastatic sites, or weakness, nausea and anorexia which may be associated with liver metastases. Although the objective response rate of chemotherapy agents is low, in an individual patient they may produce an adequate response and acceptable toxicity so that the patient experiences overall improvement in symptoms. The mainstay of chemotherapy for pancreatic cancer, as with other gastrointestinal cancers, has been fluorouracil. However, recent clinical data have shown that gemcitabine produces similar results in terms of response rate and survival, with more acceptable toxicity, so that the quality of life was judged to be better than with fluorouracil.

Pancreatic cancer provides a fertile ground for testing new, biologically based approaches to cancer therapy because of the limited success of currently available treatments.

1. Overview of Pancreatic Cancer

1.1 Initial Evaluation

Pancreatic adenocarcinoma (cancer of the exocrine pancreas) represents 95% of malignant pancreatic neoplasms.[1] Pancreatic endocrine tumours have distinct biological and clinical features which merit separate consideration[2] and are not discussed here. Although the characteristic symptoms of pancreatic cancer provide a distinctive picture, the individual features of fatigue, bodyweight loss, anorexia and vague abdominal pain are nonspecific enough that they are usually present for some time before a final diagnosis is made. Patients who present with jaundice have a somewhat better prognosis than nonicteric patients because of the possibility that a small tumour may produce biliary obstruction relatively early in its clinical course.

The optimal care plan for a newly diagnosed patient with pancreatic cancer provides a dramatic illustration of the importance of a team approach in cancer patients (table I). A small percentage of patients are potentially curable; these individuals must be identified prospectively to allow consideration of optimal treatment approaches, and incurable patients deserve to have treatment plans designed which maximise their chances of survival but respect the importance of their symptoms and quality of life. Consultation between specialists in surgery, radiotherapy (RT) and medical oncology is necessary in order to develop a plan which can be tailored to the individual patient's medical and psychosocial condition. Interindividual variations must be respected: a treatment plan which appears to one patient to be a worthwhile attempt to eradicate an otherwise fatal disease may appear to

Table I. Clinical issues in planning treatment for patients with pancreatic cancer

Metastatic disease present or absent
Technical resectability
noninvasive evaluation of operability
overall medical condition
availability of expertise to handle 'marginally resectable' patients
Biliary or intestinal obstruction present, imminent or not presently at risk
Evaluation of pain caused by tumour
Evaluation of nutritional status of patient
Evaluation of overall medical condition
Psychosocial assessment
Does a specific anticancer treatment programme have acceptable risks and benefits compared with supportive care only?

another as a 'long shot' which carries a high risk of an extended period of poor health punctuated by frequent, increasingly futile visits to the medical system. Special attention needs to be paid to symptoms of pain where present, so that the treatment plan includes either a direct intervention at the tumour site with surgery or radiation (chemotherapy alone is unlikely to cause sufficient tumour regression to alleviate pain), a tolerable programme of analgesics, or a nonpharmacological approach to pain control such as coeliac nerve block. Use of endoscopically placed stents allows nonoperative palliation of biliary obstruction.[3]

A plan for nutrition must be integrated into the medical plan because many patients have lost significant amounts of weight and may have difficulty in maintaining their nutritional status because of anorexia and nausea, liver metastases, glucose intolerance, malabsorption or gastrointestinal obstruction. This plan may include short term parenteral nutrition for the perioperative patient, surgical resection or bypass of obstructed segments of the gastrointestinal (GI) tract, supplemental enteral feeding, pancreatic enzyme supplements and/or appetite stimulants. Psychosocial and spiritual support for these patients and their families is particularly important because of the often overwhelming stress of being faced with a disease which for many patients is inexorably progressive.

1.2 Approaches to Surgery, Radiation Therapy and Combined-Modality Therapy

In general, resectable pancreatic tumours show no evidence of extrapancreatic spread, a patent superior mesenteric-portal vein confluence, and no direct extension to the coeliac axis or superior mesenteric artery when evaluated by computerised tomography (CT) scan.[1] Further improvements in noninvasive assessment of resectability may be possible in the future with newer methods such as endoscopic ultrasound, magnetic resonance imaging (MRI) and, in particular, spiral CT. The primary surgical procedure involves a radical pancreatic resection. When the tumour is in the head of the pancreas, a Whipple procedure is usually performed, and for tumours in the body or tail of the pancreas, a distal pancreatectomy is usually done. Intraoperative staging includes evaluation for metastases to the liver or peritoneum which would preclude an attempt at curative resection, and for regional nodes which can be resected along with the primary tumour. Tumour location should be marked with clips for possible future RT. Although pancreatic resection remains a formidable procedure with a significant risk of complications or prolonged recovery time, perioperative mortality in specialised centres is less than 5%, and these results appear to be superior to those in hospitals where the procedure is performed less frequently.[4] Recent series of patients undergoing pancreatic resection report 5-year survival rates in the range of 20% but, because of variations in patient selection, surgical experience and adjunctive therapies, it is not clear how predictive these results are for the centres where most of these operations are performed.[1]

External beam RT has been shown to be an important component of definitive management plans, and clearly can be useful for palliating pain from locally advanced tumours. Although the overall poor results in pancreatic cancer have stimulated the development of innovative RT approaches such as the use of radiation sensitisers, intraoperative therapy, neutron beam therapy and interstitial implants, none of these has been clearly shown to provide a major benefit over standard approaches.[5]

Combinations of fluorouracil (5-FU)–based chemotherapy and RT have been employed in the postoperative adjuvant setting, in an attempt to eradicate residual microscopic metastatic disease and in patients with localised but unresectable tumours to achieve some element of disease control and to relieve symptoms (table II). Although these combinations result in increased toxicity over the use of either modality alone, they are usually sufficiently well tolerated to justify their current wide acceptance. More recently, by analogy with other tumour types where chemotherapy and RT can produce clinical responses but surgery has been the primary therapy with curative potential, protocols have been developed which employ 'neoadjuvant'

Table II. Selected chemotherapy regimens in pancreatic adenocarcinoma if suitable clinical trial is not available

Regimen	Drug	Dosage (mg/m^2)	Regimen	Median survival (mo)
Metastatic disease				
Fluorouracil[19,25]		600	Weekly	4
Gemcitabine[25]		1000 IV bolus	Weekly × 7wk, then weekly × 3 consecutive weeks out of 4	6
FAM[6] (8wk cycle)	Fluorouracil	600 IV bolus	Weeks 1, 2, 5, 6	6
	Doxorubicin	30 IV bolus	Weeks 1, 5	
	Mitomycin	10 IV bolus	Week 1	
SMF[7] (8wk cycle)	Streptozocin	1000 IV bolus	Weeks 1, 2, 5, 6	6
	Mitomycin	10 IV bolus	Week 1	
	Fluorouracil	600 IV bolus	Weeks 1, 2, 5, 6	
Postresection adjuvant therapy[a]				
Fluorouracil[5]		500 IV bolus	Days 1-3 of each 20Gy RT segment Weekly × 2y beginning 1mo after RT	20
Locally advanced unresectable disease				
Fluorouracil[19]		350 IV bolus	Days 1-3 and last 3 days of 54Gy RT	10

a Eligibility criteria: begin therapy 4-10wk after complete resection with negative margins; adequate renal, hepatic, haematological status; adequate oral intake and stable weight for 2wk before entry.

IV = intravenous; **RT** = radiation therapy.

chemotherapy and RT followed by definitive surgery. It is hoped that the early institution of systemic therapy will improve long term survival by eliminating micrometastases and that tumour reductions produced by the presurgical therapy may improve local control results and possibly convert some 'unresectable' patients to 'resectable'.

Advanced pancreatic cancer, which is typically accompanied by liver metastases, remains one of the least tractable conditions for oncologists, with most patients surviving only a few months. Although the introduction of gemcitabine has provided a new option, the focus in these patients remains on developing an individualised treatment plan which respects the patient's wishes regarding quality of life in the context of a uniformly fatal outcome.

2. Postoperative Adjuvant Therapy

The Gastrointestinal Study Group (GITSG) reported in 1985 on a randomised, multicentre trial which compared chemotherapy and RT administered after 'curative' resection of pancreatic cancer with surgery only. They subsequently added to this experience with an additional series of nonrandomised patients treated with the same postoperative chemoradiotherapy.[8,9] Although the total number of patients was small (22 controls and 21 chemotherapy + RT patients in the randomised trial, and 30 chemotherapy + RT patients in the follow-up trial), these results remain the primary basis for standard clinical practice today. It is important to note that patients eligible for these studies had completely resected tumours with negative surgical margins and no evidence of peritoneal or other metastases. Approximately one-third of tumours were localised to the pancreas, one-third had local extension, and the remainder had local node involvement which was resected. The results of the randomised trial showed significant benefit of adjuvant therapy with respect to disease-free and overall survival, with a median survival of 20 months for chemoradiotherapy and 11 months for surgery alone. The data from longer follow-up included as part of the extension study showed that the 2-year survival rate was approximately 45% in the chemoradiotherapy-treated group and 18% in the surgery alone group. The patients were not highly selected for good performance status [43% of all patients had Eastern Cooperative Oncology

Group (ECOG) performance status 2 or 3] and severe toxicity (consisting of grade 2 leucopenia in 14% of patients) was rare.

The median survival was 29 months in a nonrandomised series of 17 patients with negative margins treated with mitomycin (mitomycin-C) 10 mg/m^2 on day 1 of RT and a 4-day continuous infusion of fluorouracil 1000 mg/m^2/day on days 1 to 4 and 29 to 32 of RT, without any further chemotherapy.[10] Toxicities did not appear to be unusually great, but details are not provided for this specific patient group. Comparison with the GITSG results is complicated by differences in the RT programmes (45-48.6 Gy in this trial *vs* 40 Gy in GITSG). In comparison with other patients treated at the same institution (including those with positive margins) with RT alone, this regimen resulted in a dramatic reduction in local recurrence rate, but there was minimal impact on overall survival.

In summary, postoperative chemoradiotherapy as administered in the GITSG study has shown a positive impact on median survival in patients with pancreatic cancer with negative margins. Although the rate of ultimately developing liver metastases was similar in the control and treated arms, the improvement in median survival suggests that this regimen has some impact on the rate of regrowth of micrometastatic disease. It is not possible to separate the relative contributions of the concurrent chemoradiotherapy and the prolonged weekly fluorouracil therapy which followed. For patients whose surgical margins are involved by tumour, it is reasonable to consider treating them in a similar fashion; however, because of the increased risks of local and systemic disease as well as the nonrepresentation of this group of patients in the GITSG trial, a careful evaluation of the potential risks and benefits is necessary before embarking on a course which may have a significant impact on their quality of life. Additional data will be available after completion of a European trial comparing postresection observation only, fluorouracil + calcium folinate for 6 months, RT with concurrent fluorouracil, and RT/concurrent fluorouracil followed by 6 months of fluorouracil/calcium folinate.[11] An important component of this trial is the prospective collection of quality-of-life data.

3. Neoadjuvant Therapy

As with bladder cancer or head and neck cancer, for which surgery has traditionally been the major curative modality but chemotherapy and/or RT can produce responses, a variety of schemas have been developed in attempts to optimise combined modality therapy. Although several pilot studies have demonstrated the feasibility of preoperative 'neoadjuvant' chemoradiotherapy, it is still too early for this approach to be adopted outside of clinical trials. In a trial of 16 patients considered unresectable on the basis of CT findings or at surgical exploration,[12] fluorouracil 225 mg/m^2/day by continuous infusion was administered concurrently with external beam RT (≥45Gy). Five patients had progressive disease, 10 underwent exploration after chemoradiotherapy (1 patient refused surgery), and only 2 had successful resection. Toxicities included grade 1 myelosuppression, grade 3 vomiting or mucositis in 3 patients, and 1 patient with severe radiation-induced gastritis. The authors postulated that because of the limited impact of this regimen on disease extent and the delay it necessitated in surgical resection, this approach should not be applied to patients with potentially resectable disease.

Another pilot trial included many (number not specified) patients with stage I or II disease,[13] and used mitomycin 10 mg/m^2 bolus on day 2 and fluorouracil 1000 mg/m^2/day for 96 hours beginning on days 2 and 28 of concurrent RT (50.4 Gy). Toxicities of this regimen, particularly GI and haematological adverse effects, were formidable (31% of patients required treatment breaks) and included severe neutropenia and thrombocytopenia. Total parenteral nutrition was required in 21% of patients. Of the patients who eventually underwent resection, almost half were alive at 24 months and only 1 of 17 pancreatic resections showed tumour involvement, suggesting a significant antitumour effect of the chemoradiotherapy.

The median survival of all patients, however, was only 9 months.

A recent multicentre trial evaluated this same preoperative regimen in a series of 53 stage I to III patients.[14] 12 patients did not undergo surgery (9 had progressive disease) and 17 were found intraoperatively to have either metastatic or locally unresectable disease. Grade 3 to 4 haematological toxicity was seen in at least one-third of the patients, biliary tract complications related to tumour or stents were common, and more than half of the patients required a period of hospitalisation before the scheduled surgery. Only 8% of patients showed objective responses on the basis of CT scans performed 3 to 4 weeks after completion of chemoradiotherapy. Median survival of the entire group was 10 months, and the 2-year survival rate of the patients who underwent surgery was 27%.

The M.D. Anderson Cancer Center in Texas reviewed their experience with pre- and postoperative chemoradiotherapy.[15] Their fluorouracil infusion–based programme was well tolerated preoperatively and toxicities did not delay the scheduled surgery. More aggressive support was required to ensure the delivery of planned therapy postoperatively. A rapid-fractionation RT schedule (30Gy over 2 weeks) was successfully employed preoperatively, which allowed the entire treatment programme to be completed in only 8 weeks. Although survival rates were similar, analysis was in favour of preoperative chemoradiotherapy because of its greater reliability in delivering the full combined modality programme, and because the additional time involved in preoperative therapy permitted the detection of metastatic disease in a group of patients who would otherwise have undergone surgery and soon afterwards developed recurrence. Another approach attempted by this group consisted of preoperative RT (30 to 50.4Gy) concurrently with fluorouracil infusion at 300 mg/m^2/day, and administering electron-beam intraoperative RT immediately following resection.[16] This series of 39 patients had a relatively low local recurrence rate, a median survival of 19 months, and a 4-year survival rate of 19%, which compares favourably with other series.

Despite the apparent positive impact of preoperative therapy in some patients, the low overall response rates and rarity of major responses limits the widespread application of this approach, even with its theoretical advantages. For a newly diagnosed patient with resectable pancreatic cancer in a nonprotocol setting, it is difficult to recommend neoadjuvant therapy as an approach that will have a significant chance of improving outcome.

4. Locally Advanced Unresectable Disease

External beam RT can produce significant palliation of pain associated with locally advanced pancreatic cancer and this modality, along with analgesic therapy including nerve blocks, forms the mainstay of the management of this group of patients. In general, combined chemotherapy and RT have shown modest improvements in median survival, with minimal if any improvement in the dismal 2-year survival rates. A landmark study by the GITSG[17] compared split-course RT alone (3 cycles of 20Gy over 2 weeks separated by 2-week rests) with RT (either 40 or 60Gy) combined with fluorouracil 500 mg/m^2 IV bolus daily for the first 3 days of each 20Gy course followed by weekly fluorouracil 500 mg/m^2 IV bolus. There was minimal difference between the 2 chemoradiotherapy arms. Although the median survival of the arms which included chemotherapy was 10 months compared with 5.5 months in the RT-alone arm, the survival curves from all 3 arms approached zero at 2 years. The chemotherapy-containing arms did not show an effect on the rate of distant metastasis, and so it was suggested by the authors that the addition of the weekly fluorouracil phase probably contributed little to the success of the regimen.

The interest in using alternative fluorouracil regimens to maximise any potential radiosensitising effects has prompted the combination of continuous infusion fluorouracil at dosages of 200 to 275 mg/m^2/day with RT.[18,19] Although this combination was well tolerated at the lower doses, the

median survivals were only 10 to 12 months. Addition of calcium folinate plus fluorouracil to RT has been tested in several combinations[20] and the authors suggest that with a radiation dose of 45Gy, fluorouracil 400 mg/m^2 IV bolus and calcium folinate 20 mg/m^2 IV bolus be given for 4 days during the first week, and for 3 days during the fifth week, of RT. In addition, this study employed a 'maintenance' regimen of fluorouracil/calcium folinate at 4 and 9 weeks after completion of RT. In this study of 22 patients, the median survival was 13.5 months, with 1 patient alive after more than 2 years.

The poor outcome of these patients, with death primarily related to metastatic disease, means that it is reasonable to ask whether local therapy is of value in addition to the small benefit provided by systemic therapy. Two randomised trials produced somewhat contradictory answers to this question. The ECOG compared weekly fluorouracil alone against RT (40Gy) plus fluorouracil given on days 1 to 3, and then weekly after completion, of RT, and observed median survivals of 8 months in both arms.[21] The GITSG studied the combination of streptozocin, mitomycin and fluorouracil administered alone or after completion of a course of RT (54Gy) together with fluorouracil (administered IV bolus on the first 3 and last 3 days of RT) and found a median survival of 8 months in the patients receiving combination chemotherapy compared with 10 months in those receiving chemoradiotherapy.[22] Only 5% of the combined modality patients had severe vomiting or diarrhoea. At least one-third of patients developed grade 3 or greater myelotoxicity, but this appears to have been seen predominantly after completion of the combined modality phase, when patients had been receiving combination chemotherapy for up to 2 years. Although the GITSG results included a significant increase in the rate of 1-year survival, the minor improvement in median survival and lesser benefit seen on longer follow-up raises the question whether any real advantage was provided by the combined modality approach.

Locally unresectable nonmetastatic disease poses a special problem in decision making. In this incurable situation associated with a median survival of well under a year, embarking on a programme of chemotherapy, RT or both in asymptomatic patients has the potential for diminishing any relatively comfortable survival time they may have. Patients who want some type of anticancer therapy should be considered for clinical trials if available, and those who are being treated outside a protocol setting should have a very frank discussion of the potential risks and benefits of therapy. In spite of the GITSG data suggesting decreased survival in patients who are treated with chemotherapy alone, the results for all treatment approaches are similar enough so that consideration of a chemotherapy-alone trial remains very reasonable. For those patients who present with symptoms from their primary disease, particularly abdominal and back pain which can be considerable, treatment plans should be centred on RT, and if the patient can tolerate the modest additional toxicities, fluorouracil alone or in combination with calcium folinate can be added. Given that the survival results from the trials of a variety of chemotherapy and RT dosages and schedules are fairly similar, the GITSG regimen[22] which combines a course of 54Gy with fluorouracil given on the first 3 and last 3 days of RT seems most convenient and tolerable, and utilises the local treatment modality which is most likely to have an impact on disease-related symptoms. In this study streptozocin, mitomycin and fluorouracil was given after completion of chemoradiotherapy, but it is difficult to make a strong case in favour of continued systemic therapy in this group of patients, in whom long term survival has been equally rare in series with or without extended chemotherapy.

5. Advanced Disease

The discouraging saga of attempts at systemic therapy for metastatic pancreatic cancer using standard chemotherapy agents is well known to oncologists and has been reviewed previously.[23] The mainstay of therapy has been fluorouracil, with estimates of response rates from various reports in the range of 15%, and little reported ben-

efit with the addition of calcium folinate, interferon-α or a combination of all three. Although small studies have suggested some benefit from combinations such as fluorouracil, doxorubicin and mitomycin (FAM) streptozocin/mitomycin/fluorouracil (SMF), fluorouracil, doxorubicin and cisplatin (FAP), and the multiagent 'Mallinson' regimen, and multicentre, randomised trials have sometimes shown improved response rates using these combinations, there has not been any meaningful impact on survival compared with fluorouracil alone. Combination chemotherapy with the Mallinson regimen was compared to supportive care only in a single-institution, randomised trial which showed median survival of 7 months in the combination chemotherapy, and 2 months in the supportive care, group.[24] This series included patients with metastatic and locally advanced disease and so there were only 7 patients with metastases in the chemotherapy group and only 8 in the supportive care group. Furthermore, a randomised, multicentre trial in which 61 patients received the same chemotherapy regimen obtained a median survival of only 4.5 months.[25] Chemotherapy with FAM has also been compared with supportive care only in a randomised, single-institution trial of 43 patients.[26] Median survival was 4 months in the supportive care group and 8 months in the FAM group. However, larger cooperative group randomised studies show median survivals in FAM-treated patients of 3 to 6 months,[1] suggesting that the reported difference between FAM treatment and supportive care might have been exaggerated by the small study size.

Gemcitabine has recently been approved for single-agent therapy on the basis of a multicentre comparison with fluorouracil 600 mg/m^2 IV bolus weekly in 126 randomised patients.[27] The median survival of the gemcitabine group (5.6 months) was significantly better than that of the fluorouracil group (4.4 months). Although neutropenia greater than grade 3 was seen in 26% of gemcitabine recipients as opposed to 5% of those receiving fluorouracil, there was no difference between the treatment groups in the incidence of serious infections. Anaemia greater than grade 3 was seen in 10% of patients given gemcitabine [a total of 27% received red blood cell (RBC) transfusions] and in none of those receiving fluorouracil (8% received RBC transfusions). Nausea or vomiting of grade 3 or greater was seen in 13% of patients receiving gemcitabine *vs* 5% of fluorouracil recipients.

Given this additional toxicity (by standard criteria), the small observed survival benefit gemcitabine clearly does not herald a major advance, but a distinctive feature of this trial was that it included a detailed analysis of quality of life with designed end-points which monitored changes in pain intensity and performance status. By these prospective criteria, 24% of patients on gemcitabine and 5% of patients on fluorouracil derived clinical benefit from therapy. The introduction of quality-of-life data into such a phase III trial added greatly to the impact of this study, but response rates in patients with measurable disease (5% gemcitabine, 0% fluorouracil) are disappointing. In spite of the low objective response rate to fluorouracil when given according to the specific schedule employed in this study, the dose-intensity of this schedule is at least comparable with those in other single-agent fluorouracil programmes and it has been accepted in the cooperative group setting.[21] It is reasonable to consider this study a fair test of the activity of fluorouracil, in the absence of randomised data comparing gemcitabine with the entire range of single-agent fluorouracil regimens. The establishment of gemcitabine in a central position for the treatment of advanced pancreatic cancer should not diminish the sense of frustration at the lack of truly effective systemic therapy for this disease, and the search for new approaches must continue.

Recently, paclitaxel has been tested in a phase II trial by the Southwest Oncology Group (SWOG).[28] A 24-hour infusion at a dosage of 250 mg/m^2 was administered every 21 days with granulocyte-colony stimulating factor (G-CSF) support to 39 patients and resulted in a median survival of 5 months, a response rate of 8%, and significant toxicities. The authors concluded that unless better results are obtained with different dosages or schedules, pacli-

taxel should be considered as having minimal usefulness in advanced pancreatic cancer.

Other recent reports of newer chemotherapeutic approaches have been published. Single agents which resulted in response rates of 10% or less with the dosages and schedules tested include topotecan,[29] doxifluridine,[30] liposomal doxorubicin,[31] the thymidylate synthase inhibitor raltitrexed,[32] extract of mistletoe[33] and fluorouracil combined with methyltetrahydrofolic acid (5-methyltetrahydrofolate).[34] In an effort to overcome drug resistance, epirubicin has been combined with dexverapamil with granulocyte-macrophage colony-stimulating factor (GM-CSF) support.[35] Although granulocytopenia and cardiac effects were seen, these appeared to be manageable and 9 of 28 patients achieved partial response, suggesting that further studies of this type should be pursued.

Although cisplatin had minimal single-agent activity,[36] several platinum-based combinations with fluorouracil (with or without calcium folinate) have been tested with only modest response rates. These included regimens with fluorouracil given as a bolus[37] or as an infusion.[38-40] Combining fluorouracil modulated by both interferon-α and calcium folinate with cisplatin resulted in 6 of 16 patients showing partial responses, but the median survival of the entire cohort was only 5 months and the toxicities were formidable.[41]

Based on the presence of luteinising hormone–releasing hormone and somatostatin receptors on some pancreatic cancer cells, 13 patients were treated with a combination of goserelin and octreotide, with one patient showing a sustained response in peritoneal metastases.[42] The investigators reviewed previous single-agent trials with these compounds, which document the rare occurrence of objective responses. Comparisons with historical controls have suggested small survival benefit without demonstrable responses in patients treated with tamoxifen,[43] but in the absence of randomised trials it is difficult to evaluate the efficacy of this drug. The matrix metalloproteinase inhibitor marimastat has been useful in laboratory models of pancreatic cancer, and early clinical trials have suggested a survival advantage over controls, particularly in patients with locally advanced disease.[44] Randomised trials with this agent and inhibitors of angiogenesis are under way.

Immunotherapy has also been attempted. Treatment with high-dose interleukin-2 plus LAK cells[45] produced no response in 8 patients. Murine monoclonal antibody 17-1A, either alone or combined with interferon-γ, has produced antitumour responses,[46] but these trials were complicated by the development of human antimouse antibodies. Clinical trials are under way with a fusion protein which combines the Fab fragment of a monoclonal antibody directed against the tumour-associated antigen CA242 (present on most pancreatic cancers) with staphylococcal enterotoxin A.[47]

Although an individual's quality of life may be improved by the institution of systemic therapy, it is clear that many patients will not benefit from this therapy, which may in fact result in deterioration of their quality of life. Careful attention to the patient's symptoms,[48] and frequent monitoring of clinical status, as well as the coping process of the patient and the family, is the most essential element of medical care for these patients. Treating physicians should be prepared to take advantage of the potential contributions from a number of specialist areas, particularly including anaesthesia for pain management consultation and nerve blocks, as well as interventional radiology and gastroenterology for nonoperative palliation of biliary obstruction. Even in the absence of effective systemic therapy, physicians should remain dedicated to providing the support of all possible resources of the healthcare system to maximise the quality of life for patients and their families.

6. Conclusions

Despite clinical trials employing many different approaches, the treatment of patients with pancreatic cancer remains a challenge to the medical community. For a small subset of patients, radical resection of the tumour followed by chemoradiotherapy is the approach which optimises the chances for extended survival. However, patients must be

carefully evaluated before embarking on this course because of the frequency of poor performance status, disease not being resectable with negative margins, or patients choosing not to pursue a treatment programme associated with substantial morbidity and only a limited possibility of long term survival. In patients with localised, unresectable disease who are symptomatic, the focus should be on palliation of symptoms, and RT, either alone or with the addition of chemotherapy, may make an important contribution. In patients with localised, unresectable disease who are asymptomatic, either close follow-up, investigational chemotherapy trials, or chemoradiotherapy could be reasonable choices, depending on discussions between the patient, their family and the medical team. For advanced disease, the end-point of any plan is symptom control, and the oncologist must be able to use all the approaches that a multidisciplinary evaluation can identify to maximise the quality of life of an individual patient.

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