The role of chemotherapy in the treatment of pancreatic carcinoma

David Goldstein, Senior Staff Specialist, Institute of Oncology, Prince Henry and Prince of Wales Hospitals, and Conjoint Associate Professor, University of New South Wales, Sydney

Summary

Patients with unresectable and metastatic pancreatic cancer are incurable and optimal palliation is the goal of therapy. If these patients have symptoms of biliary or duodenal obstruction they may benefit from palliative bypass procedures. Pain associated with local tumour infiltration may be palliated with radiation, with or without chemotherapy, or by coeliac nerve blocks or local neurosurgical procedures. Chemotherapy with gemcitabine has modest objective response rates, but can improve symptoms.

Key words: gemcitabine, palliative care.

(Aust Prescr 2005;28:42–4)

Introduction

Pancreatic cancer remains one of the most feared gastrointestinal tract malignancies. There are 1800 new cases annually and the overall median survival is 3–5 months with a 12-month survival of 10% and a five-year survival of 3%.[1,2] Pancreatic cancer is usually diagnosed late, curative surgery is rare and requires specialised expertise found in few centres.[3] It is characterised by early metastasis and resistance to all cancer treatment modalities.

The aetiology is not well understood, but risk factors thought to be associated with pancreatic cancer include smoking which increases risk twofold and chronic pancreatitis which increases the risk 5–15 fold. Hereditary cancer accounts for about 5%, but overall up to 60% of cases remain unexplained.[4]

Management of locally advanced disease (see box)

An important minority of patients present with truly localised but inoperable disease. Local control remains an important issue in this group of patients in terms of symptomatic palliation of pain, and prevention of bleeding and obstruction. These patients may benefit from palliative bypass of biliary obstruction by endoscopic, radiologic or surgical techniques. Duodenal obstruction may require a surgical bypass.

Local radiation may palliate pain associated with unresectable cancer, but it has no impact on survival. An alternative approach is the use of coeliac plexus blocks. These are associated both with improved pain control in otherwise opioid-resistant patients and in one study with increased survival.

The role of combined local radiation and chemotherapy emerged some 30 years ago. The Gastrointestinal Tumor Study Group showed a doubling in median survival with chemo-irradiation compared to radiation alone.[5] There have been several conflicting studies, but there is promise that the therapeutic ratio will improve with modern radiotherapy techniques and three-dimensional planning systems. Patients should be invited to enrol in trials of these techniques to identify optimal strategies. Ultimately it remains to be proven whether chemotherapy alone or combined therapy can give this group of patients the greatest promise of tumour control, symptom palliation and survival with less toxicity.

Management of metastatic disease

There have been major changes in the management of patients with metastases. The improvements in supportive care used to manage the symptoms of locally advanced disease have dramatically altered quality of life. The use of anabolic drugs such as megestrol acetate, dexamethasone and pancreatic supplements may also improve quality of life.

Until 1995 there was little evidence that chemotherapy provided any benefit, as the drugs were toxic and did not significantly improve survival. In randomised trials no combination regimen was superior to 5-fluorouracil (5-FU) alone, however perceptions have changed after two small randomised studies showed improved survival over best supportive care.[6,7]

Treatment options in locally advanced pancreatic cancer

- palliative surgical bypass, endoscopic or percutaneous radiologic biliary stent placement
- for pain palliation: radiation therapy with or without chemotherapy or coeliac nerve blocks/chemical splanchnicectomy/local neurosurgical procedures
- chemotherapy alone
- radiation therapy and chemotherapy with 5-fluorouracil

Investigational: radiation therapy and chemotherapy with other drugs such as gemcitabine

Gemcitabine

Gemcitabine is a deoxycytidine analogue, which is converted by deoxycytidine kinase into an active triphosphate metabolite and induces its own activation intracellularly. It has substantial anticancer activity in non-small cell lung cancer, pancreatic cancer, ovarian cancer and non-Hodgkin's lymphoma. The first study in patients with pancreatic cancer refractory to 5-FU showed a response rate of 9.5%, a six-month survival of 31%, and a median survival of 3.9 months. A subsequent initial therapy study which randomised patients to receive gemcitabine or 5-FU showed a significant increase in one-year survival (18% versus 5%) and improved quality of life specifically focusing on the issues important in pancreatic cancer, namely pain, weight loss and performance status.[8] Subsequent confirmation in a large phase IV report on over 3000 patients has reinforced this finding.[9] Gemcitabine has subsequently been studied in a large number of randomised phase III studies. These studies, involving comparisons including both 5-FU and novel therapies, have confirmed the initial data.

An overview of all the large reported phase III studies shows that after a median 3–4 cycles of chemotherapy, the response rate is 15–25%, with a median survival of 5–6.7 months and one-year survival of 18%.[10] Gemcitabine has consistently been superior to other single drugs. Attempts to improve upon this by combination with other drugs that are either synergistic in laboratory studies or other tumours have had mixed results. Neither cisplatin, nor a variety of permutations of 5-FU, nor any of a number of novel chemotherapy drugs have improved survival. As a result single drug gemcitabine remains the drug of choice for patients with metastatic pancreatic cancer who have a reasonable performance status and opt for chemotherapy.

The principal adverse effects of gemcitabine are nausea, vomiting and neutropenia. In an overview of 3000 patients only 4% discontinued because of drug-related adverse events.

New drugs

Novel targeted drugs have received extensive attention in view of the relative insensitivity of pancreatic cancer to conventional therapy. Metalloproteinase inhibitors to inhibit metastatic spread and an attempt to inhibit components of the tumour-activating pathway, such as ras, using a farnesyl transferase inhibitor have been ineffective. 5-FU in optimised schedules such as infusional 5-FU or in combination with leucovorin, or capecitabine, or new drugs such as irinotecan, does not increase survival over gemcitabine alone. Most recently, adding oxaliplatin has improved progressive-free survival, but not overall survival.[11]

Other studies have been directed at inhibition of epidermal growth factor receptor. There has also been substantial interest in the role of angiogenesis inhibitors following reports of enhanced activity in colon cancer for 5-FU and irinotecan when combined with bevacizumab – a vascular endothelial growth factor ligand inhibitor. Other receptor inhibitors are also likely to be studied given the high expression of vascular endothelial growth factor receptor on pancreatic cancer cells. Some of these are in the early stages of clinical investigation.

Although the increased activity of combination therapy has not translated into improved overall survival, response rates are reaching 30% so further studies of combinations of newer drugs are likely. Outside of clinical trials, however, single drug gemcitabine remains the chemotherapy of choice for metastatic disease.

Adjuvant therapy

Perhaps most promising are recent data suggesting an improved outlook for those patients who undergo potentially curative surgery, all of whom remain at very high risk of relapse. The European Study Group for Pancreatic Cancer (ESPAC) 1 trial is the largest adjuvant therapy study ever performed. It was built in part upon the Gastrointestinal Tumor Study Group results and also a small Scandinavian study which randomised 47 patients to combination chemotherapy and found an increased median survival of 23 months compared with 11 months for observation.

The ESPAC was a 'pragmatic' study that randomised 541 patients from 11 European countries. It had four arms with a 2 x 2 factorial design that compared the effects of adjuvant chemoradiation, chemotherapy, chemoradiation followed by maintenance chemotherapy, and observation. Just over half of the patients were randomised to the 2 x 2 factorial design, the rest were recruited to a non-factorial arm. These complexities make accurate analysis of the findings quite difficult. When all the results were pooled, adjuvant chemotherapy was superior to no chemotherapy with a median survival of 19.7 months versus 14 months ($p = 0.0005$). The 2 x 2 factorial result is also significant; the five-year survival rate was 20% in those receiving chemotherapy and 8% in those not[12], strengthening the conclusions. The study used 5-FU chemotherapy given for five days per month as a bolus injection, and this should now be regarded as the standard against which all new adjuvant studies should be performed.

Conclusion

Pancreatic cancer remains a formidable problem, but recent advances have at least resulted in a small but meaningful proportion of patients living longer. Similarly, a much larger group is now being offered a better quality of life through improved palliation. Promising new avenues of therapy are a reason for cautious optimism.

References

1. Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. Br J Surg 1995;82:111-5.

2. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002 [published erratum appears in CA Cancer J Clin 2002;52:119]. CA Cancer J Clin 2002;52:23-47.
3. Evans DB, Lee JE, Pisters PW. Pancreaticoduodenectomy (Whipple operation) and total pancreatectomy for cancer. In: Nyhus LM, Baker RJ, Fischer JE, eds. Mastery of surgery. 4th ed. New York: Little Brown and Company; 1999. p. 1233-49.
4. Talamini G, Bassi C, Falconi M, Sartori N, Salvia R, Rigo L, et al. Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. Dig Dis Sci 1999;44:1303-11.
5. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705-10.
6. Palmer KR, Kerr M, Knowles G, Cull A, Carter DC, Leonard RC. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. Br J Surg 1994;81:882-5.
7. Glimelius B. Chemotherapy in the treatment of cancer of the pancreas. J Hepatobiliary Pancreat Surg 1998;5:235-41.
8. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13.
9. Storniolo AM, Enas NH, Brown CA, Voi M, Rothenberg ML, Schilsky R. An investigational new drug treatment program for patients with gemcitabine: results for over 3000 patients with pancreatic carcinoma. Cancer 1999;85:1261-8.
10. Goldstein D, Carroll S, Apte M, Keogh G. Clinical perspectives: modern management of pancreatic carcinoma. Intern Med J 2004;34:475-81.
11. Louvet C, Labianca R, Hammel P, Lledo G, De Braud F, Andre T, et al. Gemcitabine versus GEMOX (gemcitabine + oxaliplatin) in non resectable pancreatic adenocarcinoma: Interim results of the GERCOR/GISCAD Intergroup Phase III. Proc Am Soc Clin Oncol 2003;22:250. Abstract 1004.
12. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer [published erratum appears in N Engl J Med 2004;351:726]. N Engl J Med 2004;350:1200-10.

Associate Professor Goldstein has acted as an advisor on several occasions for Eli Lilly and for other oncologic pharmaceutical companies, including Pharmacia/Pfizer, Roche, Merck AG and Novartis. He is on the board of the Australasian gastrointestinal clinical trials group and the executive of the Clinical Oncology Society of Australia. He is principal investigator on a number of current and recent trials in pancreatic cancer.

Self-test questions

The following statements are either true or false
(answers on page 51)

7. The pain of pancreatic cancer may be resistant to opioids.
8. Adjuvant therapy does not improve survival after surgical resection of pancreatic cancer.

Book review

Therapeutic Guidelines: Dermatology. Version 2.

Melbourne: Therapeutic Guidelines Limited; 2004.

410 pages. Price: $33, students $25.30, plus postage

Paul Buckley, General practitioner, Canberra

I had not read the first version of these guidelines previously, although I am familiar with other titles in the series. Having now reviewed these dermatology guidelines in detail, they will become an essential part of my therapeutic armamentarium.

The guidelines provide a thorough review of dermatological conditions, including an overview of basics, like morphology, types and distribution of lesions, and practical procedures like biopsies, intralesional steroid injections, dressings and patch testing. They include many useful tables, which provide an aide memoire for a variety of conditions and their management.

This volume is a comprehensive and up-to-date review, with detailed sections on cosmetic dermatology, drug reactions and particularly good contributions on nail disorders, eczema, vasculitis, leg ulcers and wound healing. Recently approved drugs like imiquimod for actinic keratoses and superficial basal cell cancers, and pimecrolimus for eczema are included, so the guidelines are contemporaneous.

Criticisms include the alphabetic format, the inclusion of a chapter on burns, a relatively superficial review on melanoma and the frequent recommendations for referral to a dermatologist for conditions which could be managed by a general practitioner with an interest and a little training in dermatology.

Notwithstanding, the guidelines are a very thorough, up-to-date review of most things dermatological. The index is comprehensive and the tables and boxes provide a valuable resource. The fundamentals of diagnosis and treatment, including the often overlooked basics like emollient therapy, are included.

The Dermatology Guidelines provide a valuable tool for general practitioners and students, and for those experienced in dermatology.