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Pancreatic Cancer: A Plea for More Trials

E. Van Cutsem and J. Fevery

PANCREATIC CANCER is one of the most devastating neoplasms in view of the difficulty in obtaining an early and biopsy proven diagnosis, the poor prognosis and lack of efficacy of conventional therapy. Indeed, the majority of patients with pancreatic adenocarcinoma have unresectable, incurable disease at the time of diagnosis. The survival of these patients is short, on average 3–6 months. Moreover, these patients often have severe debilitating symptoms that require palliation. Even for the minority of patients whose tumours are resected, 5-year survival is less than 20%.

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METASTATIC CANCER

Chemotherapy in metastatic pancreatic cancer has currently a purely palliative role. Although responders to chemotherapy may have survival durations that greatly exceed those of non-responders, no chemotherapeutic regimen has been demonstrated to offer a clear survival benefit for the entire group of

patients [1]. It is, therefore, extremely important to keep in mind the objectives of chemotherapy in advanced pancreatic cancer, i.e. to palliate symptoms or to delay their onset.

The poor prognosis, the severe symptomatology of pancreatic cancer and the lack of a significant effect on survival of current chemotherapeutical agents are three major points that should be considered in the decision of whether or not a chemotherapeutic treatment will be offered to patients with metastatic pancreatic adenocarcinoma.

A general appraisal of chemotherapy should comprise the questions: (1) Is a standard therapy available?; (2) Should further trials be performed?; (3) Should these trials be placebo-controlled and (4) Which further directions should be taken in the treatment of advanced pancreatic cancer?

The question of whether standard therapy is available has been examined by Lionetto and associates in this issue (pp. 882–887). Analysis of 27 randomised trials, reported during the period 1983–1993, showed that chemotherapy may be beneficial for some patients, but the most appropriate treatment regimen cannot be deduced from these studies [2]. This is due to the lack of a drug with a high activity in pancreatic cancer, and also to the surprisingly small number of randomised trials published and to the many methodological shortcomings in the published trials.

A therapy can be considered effective when it results in an appreciable number of complete tumour responses, in an extended survival for the treated population or in long-term survival with a good quality of life, even in a minority of patients. Using these criteria, no effective single chemotherapeutical agent has yet been identified [1, 2]. The development of new drugs is especially difficult in pancreatic cancer, because shrinkage of measurable lesions is used as the end-point for the initial evaluation of new drugs in phase 2 clinical trials. Peritoneal metastases are difficult to measure, and the primary cancer often grows retroperitoneally, inducing a local inflammatory reaction and fibrosis to the extent that shrinkage of the tumour after chemotherapy cannot be measured as adequately as for other tumours. The most frequently used agents are 5-Fluorouracil (5-FU), doxorubicin (epuribicin), mitomycin C, streptozotocin and cisplatin. Only 5-FU has a response rate (with 95% confidence intervals) greater than 20% [3]. More recently, it has been shown that cisplatin also has tumour-suppressing activity [4]. In general, the partial responses seen with single-agent chemotherapy are short-lived.

Several combination regimens have been shown to produce objective response rates greater than 35% in small trials and occasionally a significant prolongation of survival has been shown with one regimen when compared with supportive care [5]. The best results were initially obtained, with the FAM- and SMF-regimen, based upon 5-FU, doxorubicin and mitomycin and upon streptozotocin, mitomycin and 5-FU, respectively [6, 7]. The initial response rates of approximately 40% with this regimen, however, could not be confirmed in further studies [8]. The combination of 5-FU and cisplatin certainly warrants further investigation, since both drugs are active as single agents, and since a synergistic activity of these drugs has been reported in other tumours. At the present time, a critical analysis of randomised trials leads to the conclusion that no regimen is really superior to the other. Therefore, a standard scheme for the treatment of metastatic pancratic cancer is not available. Almost all of the actual regimens with some efficacy, however, are based upon a combination with 5-FU.

LOCALLY ADVANCED CANCER

Several studies have demonstrated that for patients with locally advanced nonresectable disease who had no distant metastases, combined-modality treatment with radiation and chemotherapy (5-FU) was clearly superior to either radiation therapy or chemotherapy alone, in terms of objective tumour responses, and also offered a small but real survival advantage [3, 9]. Severe debilitating symptoms, mainly due to local tumour growth, can be better controlled with a regimen including radiotherapy. Although the results of these trials are clear enough, the combined treatment is not performed by all clinicians, probably owing to a fear of side-effects, and due to a defeatist attitude once the diagnosis of an inoperable pancreatic cancer has been made.

FUTURE DEVELOPMENTS

How should we progress? The development of more efficient palliative strategies must be a first important goal: measures to reduce pain, to improve anorexia, cachexia and nutrition, and to improve quality of life require extensive study. Multicentric phase II trials should be planned to investigate the efficacy and value of new drugs in pancreatic cancer. For these trials, only clearly measurable metastases should be used as marker lesions for the evaluation of anti-tumour activity. Because of the relatively low efficacy of existing regimens and because of the lack of a standard regimen for metastatic cancer, further large multicentric randomised trials can be carried out with a control group receiving the best supportive care. Evaluation of quality of life and symptoms is, in these trials, almost as important as the evaluation of anti-tumour activity and of survival. In patients with locally advanced pancreatic cancer, we should try to abandon our therapeutic nihilism, since the combination of radio- and chemotherapy seems to induce a relatively high number of objective tumour responses and to offer a survival advantage [3, 9]. Therefore, questions relating to the quality of life with this combined treatment should be answered.

Future studies should certainly also be directed to an effective adjuvant treatment. The Gastrointestinal Tumour Study Group has shown that surgical resection followed by postoperative 5-FU combined with radiotherapy increases the median survival from 11 to 20 months. This regimen was not complicated by unacceptable high toxicity rates [10]. Some preliminary data also suggest that preoperative chemo-radiation and intra-operative irradiation with or without chemotherapy could possibly improve the results of surgery. Large randomised, multidisciplinary, multicentric trials are, therefore, urgently needed to evaluate the effectiveness of these different modality regimens in the adjuvant setting.

A better understanding of the regulation of normal pancreatic growth and of the mechanisms involved in malignant change of the exocrine pancreas can lead to new therapeutic applications. In this light, the role of epidermal growth factors, somatostatin analogues [11], cholecystokinin antagonists and hormonal treatment with tamoxifen [12, 13] and anti-androgens should be examined. The research of the treatment of pancreatic cancer should also be directed into newer areas such as immunotherapy and gene therapy. The roles of monoclonal antibodies as carriers of therapeutic isotopes or protein toxins, and of cytokines, such as interferons and interleukins, are under investigation. The accumulation of diverse genetic changes (mutations in the *K-ras* oncogene [14], alterations of *p53* and *DCC* tumour suppressor genes [15, 16]) in pancreatic cancer provides support for the concept of a multigenetic nature of this tumour [16]. Such

investigations will hopefully open perspectives for an earlier diagnosis of pancreatic cancer (as is the case for colorectal cancer) and might yield new therapeutical approaches.

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Problem Areas in Pain and Symptom Management in Advanced Cancer Patients

G.W. Hanks

INTRODUCTION

THERE IS one area of cancer treatment that has seen major advances in recent years, is relatively inexpensive and brings considerable gains to patients in terms of improvements in quality of life. This is the area of symptom management in patients with advanced or terminal disease.

FAILURE TO USE EXISTING KNOWLEDGE AND MEDICINE

Pain has been the usual focus of attention in the management of patients with advanced cancer because it is the most common, distressing syndrome. We have the means and the knowledge to control pain effectively in the majority of cancer patients [1]. However, many patients continue to suffer pain because the means and the knowledge are not available to their carers. Thus, the major need is not for new research to develop novel treatments, but for educational initiatives to teach the well-proven methods to all those who need to know, and political lobbying to facilitate the provision and prescription of strong opioid analgesics such as morphine. The current issue of *Cancer Surveys* [2] brings the story up to date and considers new approaches to the problem.

We have made some progress in both of these areas, but it is patchy and inconsistent. Pain in cancer can be relieved in 80–90% of patients' with pharmacological treatment [3], but the actual response rates being achieved are estimated to be no greater than 50% in Western societies and perhaps 10% in the developing world [4]. In the U.K., failure to achieve optimum results must be because of lack of knowledge—we have probably the widest range of strong opioid analgesics available and the least bureaucratic prescribing regulations. This problem is now being addressed. Every clinical medical school in the U.K. includes teaching on pain control and palliative care in the undergraduate curriculum, and in over half of these schools, students are examined on these subjects. Palliative medicine became a recognised subspeciality of general internal medical in

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