Eur J Cancer, Vol. 29A, No. 2, pp. 171–172, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00
Pergamon Press Ltd

Comments and Critique

Pancreatic Cancer: How Can We Progress?

DIFFICULTIES AND FRUSTRATION abound in the diagnosis, treatment and study of pancreas cancer. The symptoms of pancreas cancer are often vague and non-specific, and usually develop insidiously. In spite of advances in medical imaging, early diagnosis remains elusive, and patients often present with locally advanced or metastatic disease. The morbidity and mortality of pancreatic resection is high, and even for the minority of patients whose tumours are resected, 5-year survival is less than 25%. Before patients are referred to the cancer specialist, they are often cachectic or jaundiced or have ascites. Because the median age at diagnosis is approximately 70 years, many patients also have other underlying medical illnesses. The median survival of patients with metastatic pancreas cancer is approximately 3 months, and no systemic therapy has reliably yielded responses in even 15% of patients or has clearly improved survival. It is, therefore, no surprise that even among the most enthusiastic of oncologists, a nihilistic and defeatist attitude toward pancreatic cancer is pervasive. Thus, the Gastrointestinal Tract Group of the European Organisation for Research and Treatment of Cancer should be applauded for its programme of phase II evaluation of chemotherapeutic agents in patients with adenocarcinoma of the pancreas.

The obstacles encountered in evaluating antineoplastic regimens in patients with pancreatic cancer may be one reason for the lack of substantial progress in therapy. Phase II trials, designed to screen for anti-tumour activity, employ shrinkage of measurable lesions as their end-points. Not only do many patients with pancreas cancer present in a debilitated condition, limiting their tolerance of toxic therapies, but pancreas cancer often grows in a manner that is difficult to measure. Primary pancreatic masses, often considered "measurable disease" in phase II trials consist not only of malignant cells, but also include intense inflammatory reactions and fibrosis. These masses are usually poorly circumscribed and irregular in shape. Even substantial cytotoxicity to the malignant cells may not translate into a measurable reduction of tumour size, although an anti-inflammatory response to chemotherapeutic agents might result in shrinkage without having meaningful effects on the cancer. Thus, the use of a locally advanced pancreas cancer as the sole indicator of response in phase II studies may yield misleading results. The desire to have an experimental antineoplastic drug for every patient should not compromise the scientific objective of phase II investigations. Such trials should be limited to patients in good medical condition with strictly measurable lesions.

The responses observed in the EORTC trial of cisplatin are of interest[1]. The activity of cisplatin in this disease was predicted in studies of a human pancreatic cancer grown in nude mice[2]. Although the eligibility criteria of the trial required metastatic disease, 3 patients with locally advanced disease entered the trial. Appropriately, the outcome of these ineligible patients was reported, and 2 of the 3 were among the 7 responders. Given the difficulties in assessing response in such patients, what does the overall response of 21% mean? Cisplatin-based combinations have been studied in patients with pancreatic carcinoma, but most have failed to yield a high frequency of tumour regression[3–6]. Since cisplatin therapy is accompanied by potentially serious side-effects, cisplatin cannot be recommended as standard therapy in this disease, but rationally designed combinations of cisplatin with other agents, as proposed by Wils and colleagues [1], merit evaluation.

This is not to say that patients without measurable disease cannot benefit from participation in clinical trials. First, these patients are appropriate for phase I trials of promising agents and combinations. Perhaps even more important are studies that relate to the palliative care of patients with pancreas cancer. Measures to reduce pain, diminish nausea, limit other symptoms, improve nutrition, and enhance quality of life merit careful attention and thorough study. Such studies are labour-intensive, but are more important and much less costly overall than the routine use of therapies currently employed in clinical practice, be they chemotherapy alone or chemotherapy with radiation. The goals of identifying effective cytoreductive regimens and providing palliative care are complementary, not mutually exclusive. Regimens that demonstrate activity in the phase II setting should be evaluated in larger trials to better establish the true response, and to assess the impact of the treatment on survival and quality of life. The value of regimens reported to have substantial antitumour activity have been put into perspective by several such trials[6, 7].

But where do we go from here? Is the problem of developing effective therapies unique to this disease, or is it just that pancreas cancer has been insufficiently studied? Perhaps, a little of both. Our therapeutic nihilism has prevented us from studying pancreas cancer as extensively or enthusiastically as we have studied other neoplasms. Although pancreas cancer remains the fifth most common cause of cancer death in the western world, few laboratories are devoted to studying this disease. A tremendous amount of data has been amassed on the control of normal pancreatic growth and function, but relatively little is known about carcinogenesis and growth of human pancreas cancer. We are sorely lacking preclinical models for studying the biology of pancreas cancer. Rodent pancreas cancer models have provided some clues, but the relevance of these systems to the human disease has yet to be demonstrated. Nonetheless, new biological data are accumulating[8] and the advances in molecular biology are ready to be translated to clinical trials. The role of the autocrine and paracrine growth factors and their receptors is under study[9], and may present a target for new therapies. Novel hypothalamic hormone analogues with therapeutic potential are being evaluated, stimulated by the demonstration of receptors for these compounds on human pancreatic cancer[10]. Another potential window of opportunity is the observation that the majority of pancreatic adenocarcinomas express mutated K-*ras*[11], and ongoing research should lead to the development of therapeutic strategies based on the interactions of *ras* with other

proteins involved in growth regulation. Regimens derived from laboratory studies of biochemical modulation of antineoplastic agents[12] and monoclonal antibodies[13] that may serve as carriers of therapeutic isotopes or protein toxins are under active evaluation. These approaches require thoughtful preclinical development and demand careful clinical evaluation.

Will we make any progress through clincial trials? I believe that we will, but the path is likely to be long and frustrating. There will be rewards, however, for those who look to the advances in the biology of the disease, undaunted by the limited success we have had so far with empirically derived chemotherapeutic regimens.

Ephraim S. Casper
Memorial Sloan-Kettering Cancer Centre
1275 York Avenue
New York
New York 10021
U.S.A.

1. Wils JA, Kok T, Wagener DJTh, Selleslags J, Duez N. Activity of cisplatin in adenocarcinoma of the pancreas. *Eur J Cancer* 1993, **29A**, 203–204.
2. Kyriazis AP, Kyriazis AA, Yagoda A, Fogh J. Response of nude mouse-grown adenocarcinomas of the human exocrine pancreas to *cis*-diamminedichloroplatinum (II), diammine[1,1-cyclobutanedicarboxylato(2-)-O,O'-platinum], and mitoguazone dihydrochloride. *Cancer Res* 1985, **45**, 4354–4359.
3. Kelsen DP, Hudis C, Niedzwiecki D, *et al.* A phase II comparison trial of streptozotocin, mitomycin, and 5-fluorouracil with cisplatin, cytosine arabinoside, and caffeine in patients with advanced pancreatic carcinoma. *Cancer* 1991, **68**, 965–969.
4. Rothman H, Cantrell JE Jr, Lokich, J, *et al.* Continuous infusion 5-fluorouracil plus weekly cisplatin for pancreatic carcinoma. *Cancer* 1991, **68**, 264–268.
5. Kantajarian H, Ajani J, Karllin DA. *Cis*-diaminodichloroplatinum (II) chemotherapy for advanced adenocarcinoma of the upper gastrointestinal tract. *Oncology* 1985, **42**, 69–71.
6. Cullinan S, Moertel CG, Wieand HS, *et al.* A phase II trial on the therapy of advanced pancreatic carcinoma. *Cancer* 1990, **65**, 2207–2212.
7. Cullinan SA, Moertel CG, Fleming TR, *et al.* A comparison of chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. *JAMA* 1985, **253**, 2061.
8. Poston GJ, Gillespie J, Guillou PJ. Biology of pancreatic cancer. *Gut* 1991, **32**, 800–812.
9. Korc M, Chandrasekar B, Shah GN. Differential binding and biological activities of epidermal growth factor and transforming growth factor α in a human pancreatic cancer cell line. *Cancer Res* 1991, **51**, 6243–6249.
10. Srkalovic G, Cai R-Z, Schally AV. Evaluation of receptors for somatostatin in various tumours using different analogs. *J Clin Endocrinol Metab* 1990, **70**, 661–669.
11. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-*ras* genes. *Cell* 1988, **53**, 549–554.
12. Martin DS, Stolfi RL, Sawyer RC, *et al.* Application of biochemical modulation with a therapeutically inactive modulating agent in clinical trials of cancer chemotherapy. *Cancer Treat Rep* 1985, **69**, 421–423.
13. Tempero MA, Sivinski C, Steplewski Z, Harvey E, Klassen L, Kay HD. Phase II trial of interfern gamma and monoclonal antibody 17-1A in pancreatic cancer: biologic and clinical effects. *J Clin Oncol* 1990, **8**, 2019–2026.

Eur J Cancer, Vol. 29A, No. 2, pp. 172–181, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00
© 1992 Pergamon Press Ltd

Quality Assurance in Cancer Treatment

E. van der Schueren, J. Cl. Horiot, G. Leunens, R. Rubens, W. Steward, J.A. van Dongen, A.T. van Oosterom and K. Vantongelen

Report of a Working Party from the European School of Oncology

INTRODUCTION

QUALITY ASSURANCE in medicine is the process through which we attempt to monitor the actual quality of care given to an individual patient, to a patient group or to a population. When deficiencies are identified, measures taken for corrective action are formulated.

While this would seem an obvious process to be integrated in the process of health care, it appears that relatively few organised activities have taken place in this field. This is related in part to the fact that the results of health care are determined by a large number of processes and professional groups which all contribute in important ways in determining the final product. They include basic and clinical researchers, legislators, administrators, physicians and paramedical professions, each individual influence often being difficult to identify.

Apart from the complexity of the process, evaluation is also hindered by the frequent difficulty in defining adequately the aim that is pursued. For example, when considering outcome, cure is the most readily measurable parameter in statistical terms, while quality of life, palliation and patient satisfaction are difficult to quantify. It is, therefore, extremely important to define the different endpoints we need to assess. We also need to clearly identify the elements of the process to be considered separately and the mechanisms for implementing corrective action.

Different goals in quality assurance

The final value of a specific treatment can be analysed through five questions:

— is there efficacy in the treatment?
— is it effective in routine application?
— can we afford it, or does it have a good cost–benefit relation?
— is it available to all patients?
— is it applied correctly when given to a specific patient or patient group?

Correspondence to E. van der Schueren, Universitair Ziekenhuis St Rafael, Capucijnenvoer 33, BG-3000 Leuven, Belgium.
Received and accepted 24 Aug. 1992.