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Assessing Clinical Benefit in the Treatment of Pancreas Cancer: Gemcitabine Compared to 5-Fluorouracil

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An early study with gemcitabine in pancreas cancer indicated greater relief of disease-related symptoms than expected from the objective tumour response rate. A novel design was created to assess changes in symptomatology prospectively in two studies. The design focuses on typical features seen in patients with advanced pancreas cancer (pain, impaired function, weight loss) and the endpoint is 'clinical benefit response'. Traditional endpoints of objective tumour response and survival were also included. In a randomised study, the clinical benefit response rate for gemcitabine was 24% compared with 5% for 5-fluorouracil (5-FU) ($P = 0.0022$). The median survival was 5.65 months for gemcitabine compared with 4.41 months for 5-FU ($P = 0.0025$). The corresponding objective response rates were 5.4% and 0%. Disease stabilised in 39% and 19% of gemcitabine and 5-FU patients, respectively. In a second study of 5-FU-refractory patients, 27.0% of patients were clinical benefit responders. The median survival in this second study was 3.8 months; the objective response rate was 11%, and 30% of patients had stable disease. These trials show that gemcitabine improves disease-related symptoms and survival in patients with pancreas cancer. © **1997 Published by Elsevier Science Ltd. All rights reserved.**

Key words: clinical trial, gemcitabine, pancreas cancer, clinical benefit, quality of life, chemotherapy, review
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INTRODUCTION

LESS THAN 10% of patients survive a year after diagnosis of pancreas cancer. They suffer severe pain, nausea and vomiting, anorexia, weight loss and weakness as the disease progresses. Diagnosis usually occurs too late to attempt cure with surgery or radiotherapy and systemic treatment is necessary for advanced disease.

There is no standard chemotherapy regimen for the treatment of advanced pancreas cancer [1]. 5-Fluorouracil (5-FU) has been studied extensively for pancreas cancer, and response rates of up to 28% have been observed when it is used as a single agent [2]. However, responses are usually not complete and last for only a few months. Most cytotoxic drugs have been studied in pancreas cancer at some stage, but none are more effective than 5-FU. These include doxorubicin, mitomycin C, streptozotocin and cisplatin; their response rates rarely exceed 20% [2].

In the treatment of pancreas cancer, combinations of chemotherapy drugs offer little improvement over single agents. 5-FU is the basis for most combinations. Commonly used regimens included SMF (streptozotocin, mitomycin-C, 5-FU) and FAM (5-FU, doxorubicin [adriamycin], mitomycin-C [2, 3]). Initial results with these regimens were promising with response rates of up to 40% being recorded. However, further studies have not confirmed this potential. In addition, although 5-FU is generally well tolerated when used as a single agent, the toxicity of the combinations is considerably higher. As patients with pancreas cancer are often seriously debilitated, they may be unable to withstand aggressive chemotherapy.

Evaluation of new agents has relied primarily on traditional antitumour endpoints, such as reduction in tumour volume and improvement in survival. However, a mass growing in the pancreas is often poorly circumscribed and irregular in shape which makes an accurate radiographic measurement difficult. In addition, the tumour mass consists not only of malignant cells, but also of inflammatory cells and fibrosis. Objective tumour response is, therefore, difficult to assess and unreliable. This may explain the inconsistent response rates reported in trials using the same chemotherapy regimens (for example, initial response rates of 40% with the FAM and SMF regimens were not confirmed in later studies [3]).

Gemcitabine has been administered to patients with pancreas cancer in a phase II study [4]. An objective tumour response rate of 11% was recorded, but substantial improvements in disease-related symptoms were reported by both physicians and patients. Many patients required less analgesia, their functional performance status improved and they gained weight. These improvements in disease-related symptoms were anecdotal and were reported retrospectively. Therefore, studies [5, 6] were initiated prospectively to assess quality of life during gemcitabine treatment using 'clinical benefit' as an endpoint. Here we review these two papers.

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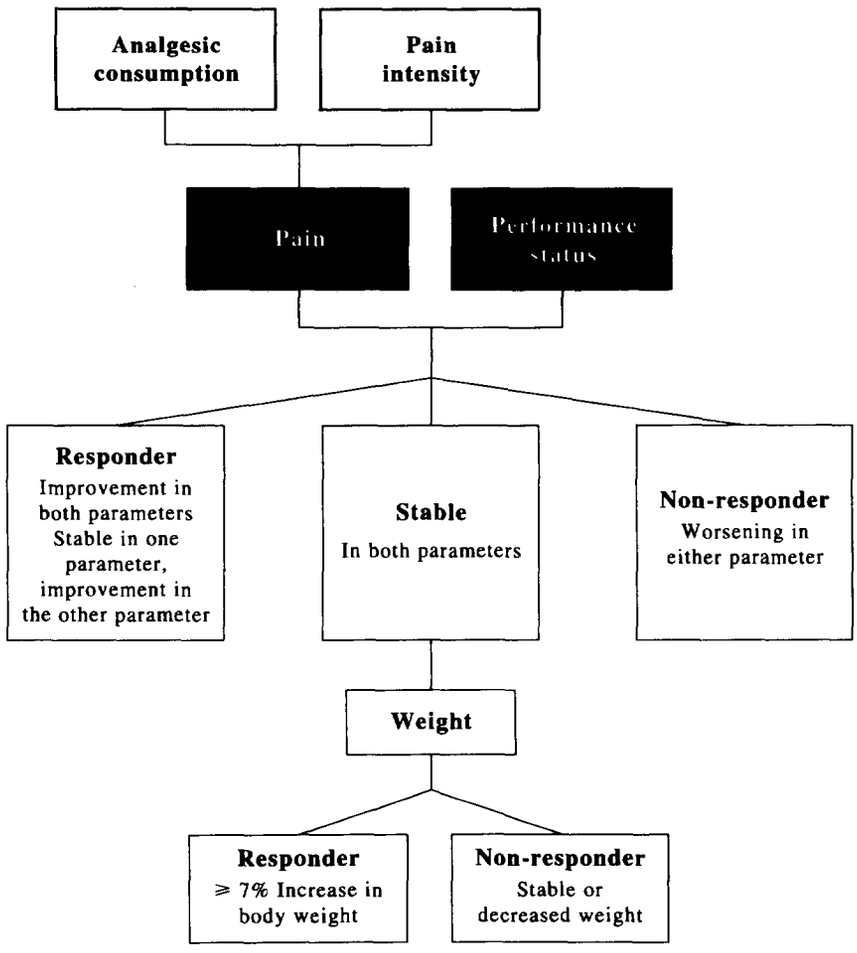

Figure 1. Assessment of clinical benefit.

MEASUREMENT OF CLINICAL BENEFIT

In both studies, clinical benefit is a composite assessment of typical debilitating symptoms of pancreas cancer [5, 6]. For patients to achieve a clinical benefit response, they have to be rated 'positive' for at least one primary parameter of pain intensity, analgesic consumption or Karnofsky performance status (KPS) but without being rated 'negative' for any of the others (Figure 1). A patient who is stable on all three primary measures can be classified as having achieved clinical benefit response only if the secondary parameter of weight is positive. A clinical benefit response represents a significant and sustained improvement in these parameters. Any pancreas cancer patient demonstrating clinical benefit would have improved to a level which would be considered remarkable for someone in this disease state.

Pain

For 2–7 days before chemotherapy started, all patients underwent a 'pain stabilisation period'. Analgesics were adjusted so that patients received acetaminophen, morphine sulphate or hydromorphone in a fixed regimen that was adequate to control their pain, and required four or fewer supplemental doses of analgesics per day to control breakthrough pain. If patients did not tolerate these particular analgesics or if their pain could not be stabilised, they did not proceed to the treatment part of the study.

Each patient was categorised as positive, negative or stable for both pain intensity and analgesic consumption. Pain intensity was assessed using the Memorial Pain Assessment Card (MPAC) [7] which each patient completed every day. It was measured on a scale of 0 (least possible pain) to 100 (worst possible pain). The weekly pain intensity measurement was calculated as the mean of the daily pain intensity scores of the previous week. A positive pain intensity i.e. reduced pain, was defined as at least 4 consecutive weeks where the pain intensity measurements were ≥50% improved from baseline. By definition, an improvement in pain was only possible where the baseline score is ≥20. Negative pain intensity i.e. increased pain, was defined as ≥4 consecutive weeks with any pain intensity measurements that were worse than baseline and exceeded 20 on the MPAC. Any pain intensity change that could not be classified as positive or negative was classified as stable.

Baseline analgesic consumption was defined as the mean analgesic consumption of the last 2 days of the pain stabilisation period. Analgesic consumption was calculated weekly as the mean of the daily analgesic consumption (expressed in terms of mg morphine-equivalents per day) for the previous week. For patients with baseline analgesic consumption ≥10 mg morphine-equivalents per day, positive (reduced) analgesic consumption was defined as ≥4 consecutive weeks with analgesic consuption ≥50% improved (i.e. reduced) from baseline. Negative (increased) analgesic consumption was defined as ≥4 consecutive weeks with any analgesic consumption that was

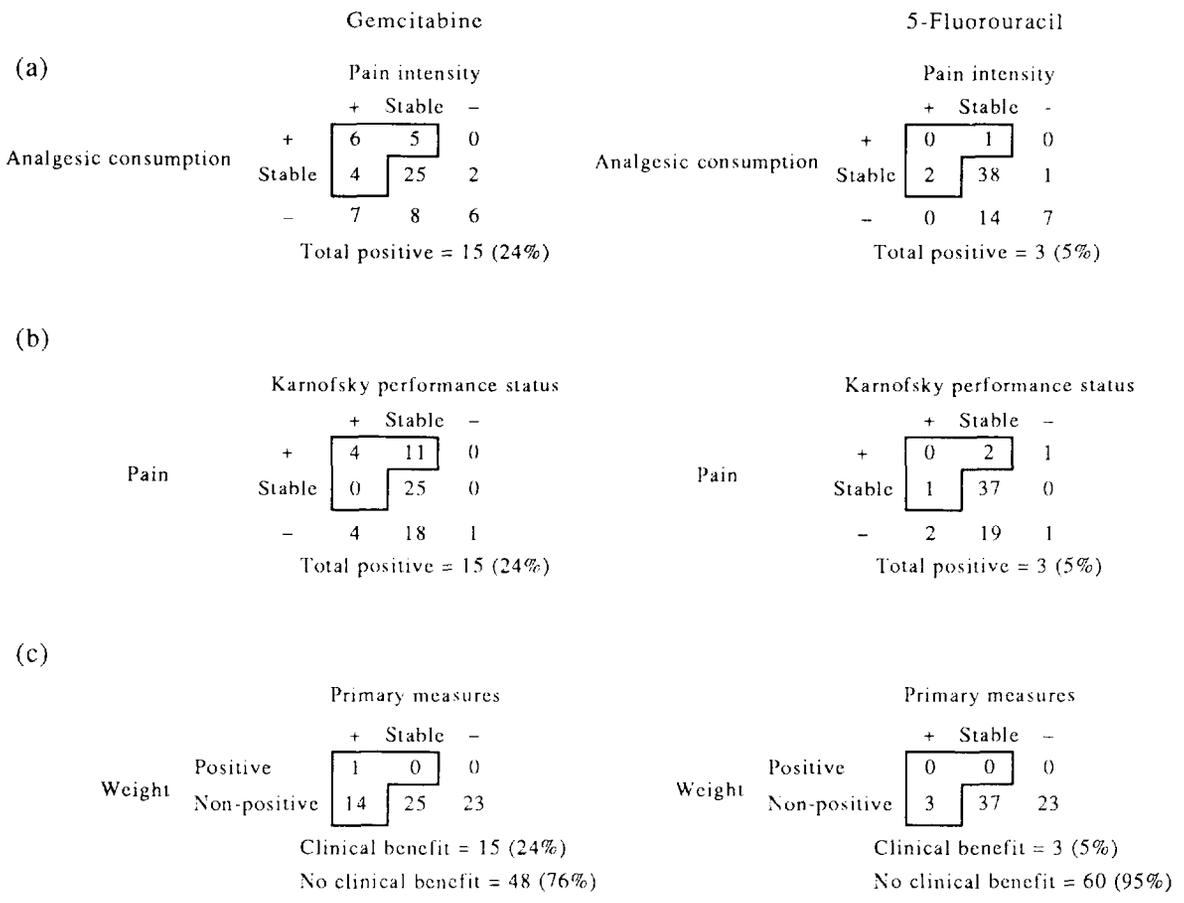

Figure 2. Clinical benefit in the randomised study comparing gemcitabine with 5-FU. (a) Pain measures; (b) primary measures of clinical benefits; (c) clinical benefit.

worse than baseline and totaled at least 10 mg morphine-equivalents per day, occurring earlier than 12 weeks after beginning treatment with the study drug. After 12 weeks, an increase in disease-related pain and other symptoms would be expected. Any analgesic consumption not classified as either positive or negative was classified as stable.

If either pain intensity or analgesic consumption was negative, then the overall pain classification was negative. However, if one of the two pain categories was positive and the other was stable, the overall pain classification was positive. If both categories were stable, then the overall pain classification was stable.

Performance status

KPS was determined by two independent blinded observers at baseline and then weekly thereafter. In cases where the scores differed, the lower of the two scores was selected. For patients with a baseline score of 70 or less, positive (improved) performance status was defined as a $\geq$20 point increase over baseline that was maintained for at least 4 weeks. Negative (worsening) performance status was defined as a decrease of at least 20 points from baseline that was maintained for at least 4 weeks and occurred during the first 12 weeks of treatment. Patients not meeting the criteria of positive or negative performance status were categorised as stable for performance status.

Weight

A patient's weight was recorded at baseline and weekly thereafter. Positive weight was defined as an increase in weight by $\geq$7% over baseline for at least 4 consecutive weeks. However, if the patient developed third-space fluid or required parenteral nutrition at any time during the study, the patient was considered non-positive for weight change. Any other change or stabilisation of weight was defined as non-positive.

Clinical benefit

A patient was considered to be a clinical benefit responder if either of the primary measures of pain or KPS was classified as positive without the other being negative. However, if either pain or performance status was negative, the patient was classified as a clinical benefit non-responder. If pain and performance status were both stable, then the secondary measures of weight change was used to determine clinical benefit (i.e. weight serves as a 'tie-breaker').

Clinical benefit has been used as the principal endpoint in two studies studying the efficacy of gemcitabine in pancreas cancer. In addition to the clinical benefit endpoint, more 'traditional' endpoints were also recorded in these studies including objective response, survival and time to progressive disease.

COMPARISON OF GEMCITABINE WITH 5-FU

Two studies have used the clinical benefit model [5, 6]. The first study was designed to compare the efficacy of gemcitabine with 5-FU in previously untreated patients with advanced or metastatic pancreas cancer [5]. A total of 126 patients, from 17 centres in Canada and the United States, were randomised to

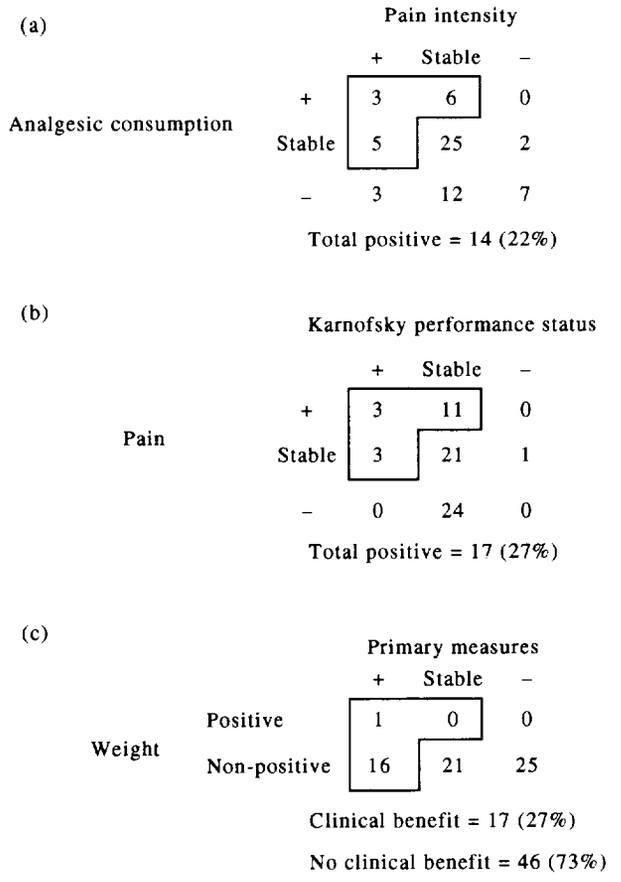

Figure 3. Clinical benefit in 5-FU refractory patients. (a) Pain measures; (b) primary measures of clinical benefit; (c) clinical benefit.

either gemcitabine or 5-FU treatment (63 to each treatment arm). Gemcitabine 1000 mg/m^2 was administered every week for 7 weeks followed by a week of rest (first cycle), then every week for 3 weeks followed by a week of rest (in subsequent cycles). 5-FU, 600 mg/m^2, was administered as a 30 min infusion once a week. Patients and performance status evaluators were blinded to treatment.

Patients on both treatment arms were balanced in terms of gender, age and disease stage. Most patients had pain at study entry: 41 (65%) on gemcitabine and 38 (60%) on 5-FU had a baseline pain intensity score over 20 points. 60 (95%) patients in each group required >10 mg morphine-equivalents per day for control of pain. A KPS of 50–70 was recorded in 44 (70%) and 43 (68%) patients randomised to gemcitabine and 5-FU treatment, respectively. All patients received at least one dose of their assigned chemotherapy.

Pain was reduced (positive) in 15 (24%) gemcitabine patients and 3 (5%) 5-FU patients. 25 (40%) gemcitabine patients and 38 (60%) 5-FU patients were classified as having stable pain (Figure 2a). When primary measures of clinical benefit were considered for gemcitabine, pain and KPS improved (i.e. 'positive') in 4 patients, and 11 patients with an improvement in pain had stabilisation of performance status score (Figure 2b). Therefore, 15 (24%) gemcitabine patients were classified as clinical benefit responders. One patient treated with 5-FU who had a positive performance status score had stabilisation of pain, while 2 5-FU patients had positive pain score with stabilisation of performance status. 2 other patients who had positive performance status scores and 1 with a positive pain score, had negative scores by other parameters and therefore were not classified as responders. Therefore, 3 (5%) 5-FU patients were clinical benefit responders as assessed by their primary measures of pain and KPS. When the secondary measure of weight was considered (Figure 2c), 1 gemcitabine patient gained sufficient weight to be classified as positive. None of the 5-FU patients could be classified as positive. However, the gemcitabine patient had already been categorised as a clinical benefit responder by primary measures. Therefore, 24% of the gemcitabine-treated patients achieved clinical benefit compared with 5% of 5-FU-treated patients ($P = 0.0022$). The median time to achieve a clinical benefit response was 7 weeks for the gemcitabine patients and 3 weeks for the 5-FU patients. The mean duration of clinical benefit was 18 weeks and 13 weeks for the gemcitabine-treated and 5-FU-treated patients, respectively. The median survival was 5.65 months with gemcitabine compared with 4.41 months for 5-FU ($P = 0.0025$). In addition the 6-, 9- and 12-month survival rates were higher with gemcitabine (46, 24 and 18%, respectively) than with 5-FU (31, 6 and 2%, respectively). The objective tumour response rate was 5.4% for gemcitabine compared with 0% for 5-FU. Disease stabilised in 39% and 19% of gemcitabine and 5-FU patients, respectively.

CLINICAL BENEFIT IN 5-FU REFRACTORY PATIENTS

63 patients were recruited to this single-arm study [6]. All patients had advanced or metastatic pancreas cancer that was not amenable to surgical treatment and had progressed despite previous treatment with 5-FU or 5-FU-containing regimens. Gemcitabine was administered as in the randomised study.

A total of 14 patients (22%) had reduced ('positive') pain during gemcitabine treatment (Figure 3a). 24 patients (38%) had increased pain intensity and/or analgesic consumption and were, therefore, considered to have 'negative' pain. 25 patients were classified as stable. Of the 11 patients with positive pain, 11 had a stable performance status and 3 had significant improvement. Of the patients with stable pain, 3 had an improvement in performance status, 21 had no change and 1 had decreased performance status. Therefore, 17 patients (27%) were considered clinical benefit responders by their primary measures of pain and KPS (Figure 3b). Of the 21 patients with no change in pain or performance status, none were classified as having a positive score for weight. Overall, 17 (27%) patients were classified as clinical benefit responders. The median time to clinical benefit response was 3 weeks and the median duration of clinical benefit response was 14 weeks. The median survival was 3.8 months with estimated 6-, 9- and 12-month survival being 31, 15 and 4%, respectively. Partial responses were observed in 6 of 57 patients with measurable disease (11%) and 30% of patients had stable disease.

DISCUSSION

The studies described in this paper demonstrate that treatment with gemcitabine relieves the pain and debilitation associated with pancreas cancer and may also increase survival. Higher clinical benefit and survival were obtained with gemcitabine than with 5-FU. The criteria used to determine clinical benefit are stringent, indicating that the improvements in symptoms are indeed remarkable for patients with this disease. The clinical benefit obtained in these studies was greater than that suggested by the objective response rate, and it is possible that a reduction in tumour size, therefore removing/reducing its

effect on adjacent tissue, may be responsible for the improvement in the patients' condition. The studies indicate that objective criteria may be used to evaluate new treatments for pancreas cancer. This model is not specific to pancreas cancer and may be adapted to use with other tumours with marked symptoms [8]. In conclusion, gemcitabine has a role in the management of pancreas cancer and should be investigated further.

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