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A phase II study of 5-fluorouracil, leucovorin and interferon-α in advanced pancreatic cancer

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Increased activity against colorectal cancer by 5-fluorouracil (5-Fu) modulation with leucovorin (LV) and/or interferon (IFN) has been reported. In this study 22 patients with measurable advanced pancreatic cancer received 5-Fu 375 mg/m² and LV 20 mg/m² by i.v. bolus daily ×5 every 28 days plus IFN-α 3 million units/m² s.c. There were three out of 21 (14%) responses lasting from 4 to 8 months. Sixteen patients (73%) had one or more episodes of grade 3 or greater toxicity (stomatitis, diarrhea or fatigue). While this combination has some activity against pancreatic cancer, its toxicity limits its potential as a palliative treatment.

Key words: 5-Fluorouracil, interferon, leucovorin, pancreatic cancer.

Introduction

There is no effective systemic therapy for advanced adenocarcinoma of the pancreas. The most active single agent is probably 5-fluorouracil (5-FU) which has a true response rate lower than 20%. *In vitro*, the cytotoxicity of 5-FU can be enhanced by a number of agents including leucovorin (LV) and interferon (IFN). LV stabilizes the binding of the intracellular 5-FU metabolite 5-fluorodeoxyuridine monophosphate (FdUMP) to thymidylate synthase (TS), leading to a more prolonged inhibition of thymidylate synthesis. Randomized studies in colorectal cancer have demonstrated improved response rates when 5-FU is combined with LV.[1] Single agent IFN-α has no significant cytotoxic activity against colonic or pancreatic adenocarcinoma. It may prevent the increase in TS production normally seen after 5-FU administration and does not appear to act by stabilizing FdUMP binding to TS.[2] The initial phase II studies of 5-FU plus IFN in colorectal cancer reported high response rates, although more recent studies have been less promising.[3,4]

Studies of 5-FU modulation in pancreatic cancer have been less frequent. Single arm studies of 5-FU plus LV have not suggested activity greater than that seen with 5-FU alone.[5] 5-FU plus IFN in the same schedule used to treat colorectal cancer demonstrated objective responses in three out of 46 (7%) patients.[6] We observed some evidence of activity against pancreatic cancer while doing a phase I study of 5-FU, LV plus IFN.[7] We therefore went on to test the maximally tolerated dose of this regimen in patients with advanced pancreatic cancer.

Materials and methods

Patient selection

Eligible patients were those with histologically confirmed adenocarcinoma of the pancreas with locally advanced or metastatic measurable disease. They had performance status (ECOG) ≤ 2, a bilirubin $< 20\ \mu M$, creatinine $< 150\ \mu M$, normal hematologic parameters and had received no prior chemotherapy.

Treatment

Chemotherapy consisted of 5-FU 375 mg/m² immediately preceded by LV 20 mg/m² both given by i.v. bolus daily ×5 days. Treatment cycles were repeated every 28 days if normal tissue toxicity had resolved. In addition to 5-FU plus LV, recombinant human IFN-α2a (Roferon-A) 3×10^6 IU/m² was given by s.c. injection daily for the 5 days of chemotherapy then three times weekly during the intervening 3 weeks. For the third and subsequent cycles the IFN was only given during

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the 5 days of chemotherapy. The 5-FU dosage in subsequent cycles was reduced by 50 mg/m^2 in patients who experienced grade 4 neutropenia (granulocytes $<500/mm^3$) or grade 3 non-hematologic toxicity, and by 100 mg/m^2 in those experiencing grade 4 non-hematologic toxicity. The IFN dosage was reduced by 25–50% in those experiencing persistent fatigue or fever. All patients gave written informed consent prior to treatment and this trial was approved by the University of Toronto Institutional Review Board.

Evaluation

Response and toxicity were assessed by standard WHO criteria.[8,9] Response assessments were made every 2 months. This always included an abdominal computed tomography scan as all patients had either pancreatic disease or liver disease. A questionnaire developed by the investigators was completed independently by patients prior to each cycle of treatment. This questionnaire asked patients to describe a number of their symptoms on an ordinal scale from 0 to 4; to rate their physical, emotional and overall quality of life, and to indicate which of the five listed ECOG categories for performance status described their status. Changes in symptoms, weight, quality of life and performance status between treatments were tested using a paired two-tailed *t*-test.

Results

Twenty-two patients were entered in the study, with all being evaluable for toxicity and 21 evaluable for response. The mean age was 56.6 years (range 41–71) with two patients being ECOG performance status 0, 13 were ECOG 1 and seven ECOG 2. The median number of courses of treatment given was three (1–8) with six patients leaving the study after one cycle (five progressive disease; one toxicity) and four receiving six or more cycles of treatment.

Toxicity

Table 1 expresses the worst degree of stomatitis, diarrhea, nausea and vomiting, and fatigue experienced by each patient while in the study. Overall 16 patients (73%) had at least one episode of grade 3 or greater toxicity. This included both 5-FU and IFN related effects and led to dosage reductions of one or both agents in six out of 16 of those who received greater than one course of chemotherapy. Loss of weight was seen in the majority of those who continued in the study. The mean weight loss over the first two cycles of therapy was 2.3 kg ($p = 0.002$). A comparison with weight loss over the 2 months preceding chemotherapy could not be made.

Table 1. Worst grade of toxicity experienced by each patient ($n = 22$)

Toxicity	≤Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis	8	5	8	1
Diarrhea	6	9	6	1
Fatigue	5	10	7	0
Nausea and vomiting	11	8	3	0

Response to therapy

Of 21 patients evaluable for response there were three (14%; 95% CI 3.0–36.3%) who met criteria for a partial response for durations of 4, 4 and 8 months. Four remained stable for 4–8 months and the remainder developed progressive disease during their first to fourth treatment cycles. The median survival was 6 months.

Analysis of symptoms from questionnaires showed a significant improvement over baseline in pain ($p = 0.003$) after one cycle of therapy that was not sustained after the second or later cycles. There was also an increase in fatigue ($p = 0.03$) and a decrease in performance status ($p = 0.03$) seen during the same interval.

Discussion

The combination of 5-FU plus LV plus IFN does have some activity against pancreatic cancer. Two other studies of this combination of agents in pancreatic cancer have been reported.[9,10] Scheithauer *et al.*[9] used 5-FU plus LV as a single i.v. bolus after 3 days of IFN (10×10^6 IU) and repeated treatments every 2–3 weeks. Responses were seen in four out of 32 patients (12.5%) and toxicity was minimal. In a preliminary report Knuth *et al.*[10] used 5-FU plus LV once weekly with IFN (9×10^6 IU) given 3 × weekly, and detected a partial response in three out of 13 patients (23%).[10] In the present study, the response rate was modest, the duration of response was short and the

treatments were poorly tolerated. Analysis of symptoms, weight and performance status showed a deterioration in performance status, fatigue and weight, but an improvement in pain. This analysis is confounded by the high frequency of progressive disease in the study. However, even amongst the seven patients who had a partial response or stable disease for four or more cycles similar degrees of weight loss and declines in performance status were seen. The wide confidence interval for the response rate raises the possibility that some activity of this combination in pancreatic cancer cannot be excluded. However, the degree of toxicity mitigates against exploring this combination further as a palliative regimen for pancreatic cancer.

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