Phase II study to evaluate combining gemcitabine with flutamide in advanced pancreatic cancer patients

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A phase II study was undertaken to determine the safety of combining flutamide with gemcitabine, with response rate being the primary end point. Twenty-seven patients with histologically proven, previously untreated, unresectable pancreatic adenocarcinoma received gemcitabine, 1 g m⁻² intravenously on days 1, 8 and 15 of a 28 day cycle, and flutamide 250 mg given orally three times daily. Treatment was halted if there was unacceptable toxicity, or evidence of disease progression. Toxicity was documented every cycle. Tumour assessment was undertaken after cycles 2 and 4, and thereafter at least every additional four cycles. One hundred and seventeen cycles of treatment were administered, median four cycles per patient (range 1 – 18). Gemcitabine combined with flutamide was well tolerated, with most toxicities being recorded as grade 1 or 2 and only nine treatment cycles associated with grade 3 toxicity. The most frequent toxicity was myelosuppression. One case of transient jaundice was recorded. The commonest symptomatic toxicity was nausea and vomiting. The response rate was 15% (four partial responses), median survival 6 months and 22% of patients were alive at 1 year. These results suggest antitumour activity of the combination therapy to be equivalent to single agent gemcitabine.

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Pancreatic cancer is the fifth most common cause of adult death from malignancy, being responsible for nearly 5% of all cancer deaths. Unfortunately, to date, over 80% of patients at diagnosis present with advanced disease not amenable to surgery and their median life expectancy is around 4 months (Kelly and Benjamin, 1995). Pancreatic adenocarcinoma is both chemo- and radioresistant, with few single agent chemotherapy drugs achieving a response rate above 10%. In the pivotal prospective multicentre randomised trial comparing the doxorubicin analogue, gemcitabine (2’-difluorodeoxycytidine, Gemzar; Eli Lilly and Co. Ltd), 1 g m⁻² 30 min infusion given weekly, with 5-fluorouracil (5FU), 600 mg m⁻² 30 min infusion given weekly, in previously untreated pancreatic cancer patients (Burris et al, 1997), response rate, median survival and 1 year survival were 5.4%, 5.65 months and 18% for the gemcitabine arm, compared with 0%, 4.41 months and 2% for the 5FU arm. More clinically meaningful effects on disease-related symptoms (pain control, performance status and weight gain) were seen in gemcitabine-treated patients, with 24% achieving a clinical benefit response compared with only 5% of 5FU-treated patients. Despite these limited patient benefits, gemcitabine is now internationally accepted as standard systemic chemotherapy for such patients with unresectable disease. However, there is a clear need to identify more effective treatments.

Recently, a small single centre randomised placebo-controlled trial of the oral antiandrogen, flutamide, in unresectable pancreatic cancer was published (Greenway, 1998). Median survival was 8 months in the flutamide arm and 4 months in the placebo arm. Excluding patients who progressed within 6 weeks of treatment, these figures were 12 and 5 months respectively. These results support some preclinical data suggesting that testosterone may be a growth factor for pancreatic cancer. Androgen receptors have been demonstrated in human pancreatic cancer tissue (Corbishley et al, 1986), together with the steroid synthetic enzymes, aromatase and 5α-reductase (Iqbal et al, 1983). In addition, patients with pancreatic cancer appear to have low serum testosterone concentrations (Greenway et al, 1983). Finally, testosterone has been shown to promote the growth of human pancreatic adenocarcinoma xenografts grown in nude mice, while an antiandrogen inhibited this effect (Greenway et al, 1982). Greenway’s trial of 49 patients has been criticised for its small size and histological evidence of the disease was obtained in only 35% of cases. Even so, the suggestion that androgen receptor blockade may significantly improve survival of pancreatic cancer patients warrants further testing. Furthermore, the potential to combine flutamide with gemcitabine is attractive, since each single agent has a side effect profile acceptable for pancreatic cancer patients who are frequently elderly, frail and plagued with disease-related symptoms. We therefore undertook a phase II study to evaluate the combination regimen of gemcitabine and flutamide for safety, tolerability and efficacy.

PATIENTS AND METHODS

Patient eligibility

The eligibility criteria were histological or cytological diagnosis of previously untreated, unresectable (locally advanced or metastatic) pancreatic adenocarcinoma. Patients with previously resected disease who had received adjuvant therapy could be entered if
relapse occurred more than 6 months from the date of completing previous therapy. Measurable disease was required, defined as evidence of any tumour mass which could be measured bidimensionally either clinically or radiologically. Baseline CT scans were performed within 4 weeks prior to commencing treatment. Patients had to be at least 18 years of age, with Eastern Cooperative Oncology Group performance status (PS) ≤2. Laboratory parameters were as follows: HB ≥10 g dl⁻¹, platelets ≥100 000 mm⁻³, ANC ≥1500 mm⁻¹; bilirubin <1.3 × ULN, Alk phos <2.5 × ULN, transaminases <2.5 × ULN; serum Creatinine <1.5 × ULN. Patients could be entered beyond 7 days after major surgery or 3 days after laparoscopy. All patients gave written informed consent and the study was approved by the local research ethics committees of the three participating UK centres: Addenbrooke’s Oncology Centre, Cambridge, the Churchill Hill Hospital, Oxford, and the Hammersmith Hospital, London.

Systemic therapy
Gemcitabine was administered as a 30 min infusion, 1 g m⁻² weekly on days 1, 8 and 15, for 3 consecutive weeks, on a 4 week cycle. Flutamide was commenced on day 1 and taken orally 250 mg three times daily. Toxicity was assessed using the National Cancer Institute common toxicity criteria. Gemcitabine was halted if grade 3 or more nonhepatic toxicity occurred, and recommenced on recovery at 25% reduced dose. Treatment was halted for grade 2 or more liver toxicity. On recovery to grade ≤1, gemcitabine was restarted at full dose, but flutamide was reduced to 250 mg twice daily in the case of grade 2 liver toxicity and omitted altogether in the case of grade 3 liver toxicity.

The initial study treatment period was defined as four cycles in the first instance. Patients completing cycle 4 with stable or responding disease and without significant side effects were allowed to continue treatment if they wished. Treatment was discontinued if there was unacceptable toxicity, evidence of disease progression, at patient request, or if considered appropriate for any other reason by the patient’s doctor.

Study parameters
Physical examinations, PS, weight, blood count, renal and liver function tests were measured at baseline and on days 1, 8 and 15 of every 4 week cycle. Serum CA19.9 was measured at baseline and if raised, was repeated every 4 weeks. Baseline serum testosterone was also measured. Tumour assessment for measurable disease was performed within 4 weeks of commencing treatment. This was repeated after cycle 2 and 4 and thereafter, at least every four cycles. An initial chest X-ray was performed and repeated when appropriate, at least every 6 weeks of treatment and 10 were assessable for response on completion of cycle 2. For the whole study population (n=27), the objective response rate was 15% (4 PRs). Of the remaining patients, 13 (48%) had stable disease of duration ranging between 14 and 76.3 weeks, with median 35.3 weeks. Ten (37%) patients had progressive disease documented at the first assessment. The objective PRs occurred in two patients with locally advanced and two patients with disseminated disease, involving the liver in one case and left supraclavicular and axillary lymphadenopathy in the other. Responses were documented after cycle 2 in three cases and cycle 4 in one case. These responses were sustained for 6, 8, 27 and 16 weeks, respectively.

Toxicity
All patients were evaluated for toxicity. The median number of cycles of combination therapy received was 4, with range 1–18.
Toxicity documented every cycle was generally mild (Table 2). However, haematological grade 3 toxicity was documented on five occasions, comprising neutropenia in three cases and anaemia in two cases. Thrombocytopenia was only ever documented as grade 1 or 2 and occurred on five occasions. One case of grade 3 liver toxicity (jaundice) occurred, which appeared to resolve on stopping flutamide. Three cases of symptomatic grade 3 toxicity were documented, comprising nausea and vomiting in two cases and skin rash in one case. The most frequently documented symptomatic grade 1/2 toxicities were fatigue (11 cases), nausea and vomiting (nine cases) and diarrhoea (five cases).

Sixteen patients had no modification of their treatment doses while on study. Modifications were made because of toxicity attributable to gemcitabine in eight patients and to flutamide in three patients. Reasons given for gemcitabine modification were haematological toxicity or severe skin rash, requiring three patients to stop gemcitabine treatment entirely. Flutamide was modified due to hot flushes or nausea, and in one patient who became jaundiced shortly after starting combination treatment, no treatment required to identify an antitumour effect of flutamide before further clinical trials in pancreatic cancer could be justified.

In conclusion, it appears that gemcitabine may be safely combined with flutamide. The combination regimen appears to be at least as effective as, although probably not superior to single agent gemcitabine. Although testosterone was not measured in all study patients, the data does not support a previous report suggesting that all pancreatic cancer patients have low serum testosterone levels. In this study, no liver-related side effects were reported (Shaw et al, 2000). The results of this study demonstrate that gemcitabine can be safely combined with flutamide in patients with advanced pancreatic adenocarcinoma. Few grade 3 and no grade 4, life threatening, toxicities were recorded. In a single patient who became jaundiced shortly after starting combination treatment, omission of flutamide led to resolution of liver blood tests and the patient was able to continue treatment with gemcitabine alone. 60% of patients were able to tolerate full doses of treatment without significant toxicity. Of those whose treatment was modified, the majority required dose reduction of gemcitabine for reasons predicted by the known side effect profile of this drug. There was no indication that combination therapy potentiated risk of toxicity from either drug.

The response rate associated with this treatment combination was 15%. This and the median survival of 6 months equate well with other phase II study data becoming available for gemcitabine-based combination regimens (Louvet et al, 2002), although many of these cytotoxic regimens are associated with more drug-related toxicity than described in this study.

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