A phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with locally advanced pancreatic cancer

M Ikeda1, S Okada*,1, K Tokuyue2, H Ueno1 and T Okusaka1

1Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; 2Radiation Oncology Division, National Cancer Center Hospital, Tokyo, Japan

This study investigated the maximum-tolerated dose of gemcitabine based on the frequency of dose-limiting toxicities of weekly gemcitabine treatment with concurrent radiotherapy in patients with locally advanced pancreatic cancer. Fifteen patients with locally advanced pancreatic cancer that was histologically confirmed as adenocarcinoma were enrolled in this phase I trial of weekly gemcitabine (150–350 mg m⁻²) with concurrent radiotherapy (50.4 Gy in 28 fractions). Gemcitabine was administered weekly as an intravenous 30-min infusion before radiotherapy for 6 weeks. Three of six patients at the dose of 350 mg m⁻² of gemcitabine demonstrated dose-limiting toxicities involving neutropenia/leukocytopenia and elevated transaminase, while nine patients at doses of 150 mg m⁻² and 250 mg m⁻² did not demonstrate any sign of dose-limiting toxicity. Of all 15 enrolled patients, six patients (40.0%) showed a partial response. More than 50% reduction of serum carbohydrate antigen 19-9 level was observed in 13 (92.9%) of 14 patients who had pretreatment carbohydrate antigen 19-9 levels of 100 U ml⁻¹ or greater. The maximum-tolerated dose of weekly gemcitabine with concurrent radiotherapy was 250 mg m⁻², and this regimen may have substantial antitumour activity for patients with locally advanced pancreatic cancer. A phase II trial of weekly gemcitabine at the dose of 250 mg m⁻² with concurrent radiotherapy in patients with locally advanced pancreatic cancer is now underway.

Keywords: pancreatic cancer; gemcitabine; chemoradiotherapy; CA19-9

Pancreatic cancer (PC) is diagnosed at an advanced stage in most patients, despite recent improvements in diagnostic techniques. Among these patients, roughly half are diagnosed with locally advanced disease radiographically confined to the pancreas and surrounding tissues (Okada, 1999). In the patients with locally advanced PC, prospective randomized trials conducted by Moertel et al. (1969) and the Gastrointestinal Tumor Study Group (GITSG) (Moertel et al., 1982; Gastrointestinal Tumor Study Group, 1988) have demonstrated that the combination of radiotherapy and chemotherapy (chemoradiotherapy; CRT) resulted in significantly better survival than either radiotherapy alone or chemotherapy alone. In patients with resectable PC, the randomised controlled trial conducted by GITSG demonstrated a significant survival advantage for patients receiving adjuvant CRT (Gastrointestinal Tumor Study Group, 1987), but the European Study Group for Pancreatic Cancer (ESPAC) trial failed to show the survival benefit of adjuvant CRT (Neoptolemos et al., 2001). Thus, CRT is presently accepted as the standard treatment for locally advanced PC (Okada, 1999), but the role of adjuvant CRT for patients with resectable PC remains controversial. However, optimal CRT regimens have not yet been determined, although various anticancer agents and radiation schedules are being examined in clinical trials.

Gemcitabine is a novel deoxycytidine analogue with a broad spectrum of antitumour activity against a variety of solid tumours including PC (Abratt et al., 1994; Casper et al., 1994). In patients with advanced PC, gemcitabine demonstrated a greater clinical benefit and survival compared with 5-fluorouracil (Bruiss et al., 1997). Gemcitabine has also been shown to be a potent radiosensitizer in human pancreatic and other solid tumour cell lines (Lawrence et al., 1996; Shewach and Lawrence, 1996; van Putten et al., 2001), suggesting that the combination of radiotherapy and gemcitabine may improve survival in patients with locally advanced PC. Therefore, we conducted a phase I trial to determine the maximum-tolerated dose (MTD) of gemcitabine based on the frequency of dose-limiting toxicities (DLT) of weekly gemcitabine treatment with concurrent radiotherapy in patients with locally advanced PC.

PATIENTS AND METHODS

Eligibility

Patients eligible for study entry had histologically or cytologically confirmed locally advanced non-resectable PC. Eligibility criteria were: 20–74 years of age; Karnofsky performance status of 50–100 points; no evidence of distant metastasis, measurable or assessable disease, an estimated life expectancy ≥ 8 weeks after study entry; no prior treatment for PC; adequate haematological function (haemoglobin ≥ 10 g dl⁻¹, leukocytes ≥ 4000 mm³, neutrophils > 2000 mm³, and platelets ≥ 100 000 mm³), adequate hepatic function (serum total bilirubin ≤ 2.0 mg dl⁻¹ and serum transaminases (glutamic oxaloacetic transaminase (GOT)/glutamic pyruvic transaminase (GPT)) ≤ 2.5 times upper normal limit
Toxicity and response evaluation

The primary end-point of this trial was to evaluate the frequency of DLT, and the secondary end-point was to evaluate the potential antitumour activity. Treatment related toxicities were assessed using National Cancer Institute – Common Toxicity Criteria version 2.0. During CRT, complete blood count with differential, serum chemistry, and urinalysis were measured at least once a week. Tumour response was evaluated at the completion of CRT and thereafter every 8 weeks until tumour progression, according to the standard World Health Organization criteria (Miller et al, 1981). Serum carcinoembryonic antigen levels (CEA) and serum carbohydrate antigen 19-9 levels (CA19-9) were measured monthly by an immunoradiometric assay. This phase I study was approved by the Institutional Review Board of the National Cancer Center.

RESULTS

Patients characteristics

Fifteen patients were enrolled in this study from May 2000 to April 2001 at the National Cancer Center Hospital, Tokyo, Japan. The characteristics of the patients are listed in Table 1. The median age was 59 (range: 51 – 74) years. Karnofsky performance status was 100 in one patient (7%), 90 in 13 (87%), and 80 in 1 (7%). The median serum CA19-9 level is 1109 (range: 6 – 16780). Patients were treated with radiation and concurrent weekly gemcitabine over three dose levels, as listed in Table 2.

Toxicity

The toxicities observed in the 15 enrolled patients are listed in Table 3. There was no treatment-related death during this study. Three of six patients treated at the gemcitabine 350 mg m⁻² dose level experienced DLT; one patient developed grade 4 leukocytopenia/neutropenia, a second developed grade 4 serum GPT increase, and a third required two successive weeks’ omission of gemcitabine administration due to serum GOT and GPT increase. Moreover, before DLT was observed in level 1, 8 of 31 planned administrations were omitted due to adverse effects including leukocytopenia, neutropenia, GOT/GPT increase, and severe fatigue. Because the DLTs were observed in three of six patients at the first dose level (350 mg m⁻²), the protocol was revised and subsequent patients were enrolled at lower dose levels (gemcitabine dose level –1: 150 mg m⁻², level 0: 250 mg m⁻²). Six patients were enrolled in level 0 to evaluate the frequency of DLT more accurately, although no DLT was observed in the initial three patients. One of 18 planned administrations at level –1 and 4 of 36 administrations at level 0 were omitted due to adverse effects, including grade 3 leukocytopenia, grade 3 neutropenia, grade 3 thrombocytopenia, and grade 3 GOT/GPT increase which did not exceed 10 times UNL. However, these toxicities were mild and transient, and all patients treated at level –1 or level 0 completed the scheduled course of CRT without DLT. Gastric ulcer with epigastralgia was observed in one patient (level 0) 1 week after CRT, but the patient recovered with medical treatment using omeprazole (Omepral; Astra Zeneca, Sweden). Thus, weekly gemcitabine at a 150 mg m⁻² or a 250 mg m⁻² dose was considered well tolerated.

Response

Six patients (level 1: 4 patients, level –1: 0 patients, level 0: 2 patients) achieved partial response, giving an overall response rate of 40.0% (95% confidence interval, 15.2 – 64.8%), and the mean duration of response was 7.5 months (range: 3.3 – 12.3 months). The remaining nine patients demonstrated stable disease. After the completion of CRT, the serum CA19-9 level was reduced more than 50% in 13 (92.9%) of 14 patients who had shown a pretreat-
DISCUSSION

Currently, concomitant external beam radiotherapy and chemotherapy has been accepted as the standard therapy for patients with locally advanced unresectable PC (Okada, 1999), because randomized trials have demonstrated improved survival with CRT compared with that by either radiation alone or chemotherapy alone (Moertel et al, 1988; Gastrointestinal Tumor Study Group, 1988), although the role of adjuvant CRT for patients with resectable PC remains controversial. To intensify treatment efficacy, various anticancer agents, and radiation schedules are being examined in clinical trials. However, to date, optimal CRT regimens have not yet been determined.

Gemcitabine produced significantly better clinical benefit (decreased pain, improved performance status and/or weight gain) (response rate, 23.8% vs 4.8%) and survival advantage (median survival, 5.6 vs 4.4 months) compared with bolus 5-fluorouracil in a phase III trial (Burris et al, 1997), and the similar effects on disease-related symptoms were documented in patients with 5-fluorouracil-refractory PC (Rothenberg et al, 1996). Moreover, in over 3000 patients with advanced PC treated with gemcitabine, notable disease-related symptom improvement (response rate, 18.4%) and survival (median survival, 4.8 months) were also seen (Storniolo et al, 1997). Therefore, gemcitabine has recently been accepted as the first-line chemotherapy for advanced PC, particularly in Western countries. In the majority of reported clinical trials including these trials, gemcitabine was administered once weekly. Gemcitabine has also been demonstrated in vitro and in vivo to enhance the cytotoxic activity of radiation (Lawrence et al, 1996; Shewach and Lawrence, 1996), although the precise mechanism of radiosensitization remains unknown (van Putten et al, 2001). Some clinical trials of gemcitabine and concurrent radiotherapy have been reported (Blackstock et al, 1999; Talamonti et al, 2000), but the optimal dosage for a weekly gemcitabine schedule has not yet been elucidated. Although it has been reported that a twice-weekly schedule of gemcitabine is superior to a once-weekly schedule of gemcitabine for radiosensitization (Blackstock et al, 1999), the dose of gemcitabine was much lower (40 mg m⁻², twice-weekly) than that used for systemic chemotherapy. In patients with locally advanced PC treated with CRT, it is important to enhance the local control and simultaneously reduce the risk of distant metastases. Therefore, this phase I trial was designed to determine the MTD of weekly gemcitabine with concurrent radiation in patients with locally advanced PC. Eligibility criteria of this trial included Karnofsky performance status of 50 – 100 points. However, all enrolled patients had the Karnofsky performance status of 80 or above, because the patients with poor performance status (e.g. Karnofsky performance status of less than 70) were considered to be intolerable to CRT for fear of the treatment-related toxicities such as fatigue.

We expected that the dose of weekly gemcitabine with concurrent radiotherapy would be close to 1000 mg m⁻², which is the standard dose for weekly gemcitabine administration for PC. However, DLTs involving neutropenia/leukocytopenia and elevated transaminase were observed in three of six patients at the first dose level (350 mg m⁻²), and the protocol was therefore revised to...
include lower dose levels (150 and 250 mg m\(^{-2}\) per week). All nine patients treated at the dose of 150 or 250 mg m\(^{-2}\) per week of gemcitabine completed the scheduled course of CRT with no DLT. In this CRT, the most common toxicities were leukocytopenia and/or neutropenia. However, these toxicities were mild and transient at level 1 and level 0, and all patients recovered within a week without any specific treatment for these toxicities. Anorexia and/or nausea observed on the day of gemcitabine administration were the major non-haematological toxicities. However, these toxicities were relieved by prophylactic use of granisetron on subsequent administration of gemcitabine. Serum GOT/GPT increase observed at level 0 (250 mg m\(^{-2}\)), which was another major non-haematological toxicity, was also mild and transient. Therefore, weekly gemcitabine at a dose of 150 mg m\(^{-2}\) or 250 mg m\(^{-2}\) was considered well tolerated, and the MTD was determined to be 250 mg m\(^{-2}\).

With regard to antitumour activity of weekly gemcitabine with concurrent radiation, 6 out of 15 patients achieved partial response, giving an overall response rate of 40.0% (95% confidence interval, 15.2 – 64.8%). Moreover, the serum CA19-9 level was reduced more than 50% after the completion of CRT in 13 (92.9%) of 14 patients with a pretreatment level of 100 U ml\(^{-1}\) or greater. These results are favourable compared with those of patients treated with CRT at other treatment schedules (Moertel et al, 1969, 1981; Gastrointestinal Tumor Study Group, 1988; Ishii et al, 1997; Blackstock et al, 1999; Talamoto et al, 2000; Okusaka et al, 2001). To date, however, there are no data on overall survival and progression-free survival because of the short follow-up periods. Phase II trial is required to clarify the antitumour activity and the effect of weekly gemcitabine with concurrent radiation on survival.

In conclusion, the MTD of weekly gemcitabine with concurrent radiotherapy was 250 mg m\(^{-2}\), and this regimen may have substantial antitumour activity for patients with locally advanced PC. A phase II trial of weekly gemcitabine at a dose of 250 mg m\(^{-2}\) with concurrent radiation in patients with locally advanced PC is now underway.

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