Gemcitabine plus CI-994 offers no advantage over gemcitabine alone in the treatment of patients with advanced pancreatic cancer: results of a phase II randomized, double-blind, placebo-controlled, multicenter study


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Background: CI-994, an oral histone deacetylase inhibitor, has antineoplastic activity and synergism with gemcitabine preclinically. This randomized phase II trial explored whether CI-994 plus gemcitabine improves overall survival, objective response, duration of response, time to treatment failure and change in quality of life (QoL) or pain compared with gemcitabine alone.

Patients and methods: A total of 174 patients received CG (CI-994 6 mg/m²/day days 1–21 plus gemcitabine 1000 mg/m² days 1, 8 and 15 each 28-day cycle) or PG (placebo plus gemcitabine 1000 mg/m² days 1, 8 and 15 of each 28-day cycle days 1–21).

Results: Median survival was 194 days (CG) versus 214 days (PG) (**P** = 0.908). The objective response rate with CG was 12% versus 14% with PG when investigator-assessed and 1% versus 6%, respectively, when assessed centrally. Time to treatment failure did not differ between the two arms (**P** = 0.304). QoL scores at 2 months were worse with CG than with PG. Pain response rates were similar between the two groups. There was an increased incidence of neutropenia and thrombocytopenia with CG.

Conclusions: Adding CI-994 to gemcitabine in advanced pancreatic carcinoma does not improve overall survival, response rate or time to progression; CG produced decreased QoL and increased hematological toxicity and appears inferior to single-agent gemcitabine.

Key words: gemcitabine, histone deacetylation inhibitor, metastatic disease, pain, pancreatic cancer, placebo, quality of life

introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States. Nearly 33 730 new diagnoses of pancreatic cancer will occur in the USA in 2006, with an estimated 32 300 deaths [1]. The disease has an overall mortality incidence of 98% [2]. Historically, chemotherapy has been a minimally effective treatment modality with 5-fluorouracil (FU) having been the standard of care for many years [3–5]. In the late 1990s, gemcitabine, a novel nucleoside analog, had demonstrated modest reproducible activity in this disease. A phase III trial of patients with advanced pancreatic cancer demonstrated that gemcitabine produces improved outcomes compared with 5-FU in terms of overall survival, time to tumor progression (TTP), objective response and, most importantly, subjective patient benefit [6, 7]. Worldwide, gemcitabine then became the chemotherapy agent of choice in patients with advanced pancreatic cancers, despite its low response rates.

Despite modest advances, pancreatic cancer remains a disease greatly in need of improved treatment outcomes. Because gemcitabine is generally well tolerated, it is logical to attempt to improve its single-agent activity by combining it with other novel therapeutic agents.

CI-994 [4-(acetylamino)-N-(2-aminophenyl)benzamide] is a novel oral compound with an unusual spectrum of antitumor activity in preclinical models. Refractory tumors
tend to be sensitive to CI-994, whereas tumors sensitive to conventional agents tend to be refractory to CI-994 [8]. CI-994’s mechanism of action involves inhibition of histone deacetylation and may be unique among existing clinically effective anticancer agents [9]. Histone deacetylation inhibitors arrest tumor growth, inducing differentiation and/or apoptotic death [10]. Several in vivo experiments have been conducted combining CI-994 with other cytotoxic agents including gemcitabine [11]. In these experiments, mice previously implanted with LC12 squamous cell carcinoma were treated with optimum doses of CI-994 alone, gemcitabine alone, or the combination of these agents given either sequentially or simultaneously. Synergism was demonstrated by the administration of gemcitabine with CI-994. Increased response rates and long-term tumor-free survival resulted from the combination compared with single-agent dosing. Phase I trials of CI-994 were conducted in patients with solid tumors using a dose escalation scheme, increasing both the daily dose and the duration of therapy [12, 13]. The maximum tolerated dose (MTD) was 15 mg/m²/day on days 1–14. The dose limiting toxicities (DLT) were thrombocytopenia and/or neutropenia, usually during cycle 1. To allow more prolonged treatment, lower doses were studied using 8 weeks of daily therapy followed by a 2-week drug holiday. The MTD was 8 mg/m²/day. Toxicities included nausea, vomiting, diarrhea, anorexia, fatigue, mucositis, headaches, dehydration and abnormal liver and renal function values. Although not a study objective, a partial response (PR) was observed in one heavily-pretreated patient with non-small-cell lung cancer [14].

A small phase II trial of CI-994 in advanced pancreatic cancer has been conducted in 17 patients, resulting in no objective responses [15]. CI-994 was well-tolerated; the most common adverse events were thrombocytopenia and neutropenia. In other phase II trials of CI-994, two of 29 patients with NSCLC and one of nine patients with head and neck cancer achieved a PR following treatment with CI-994 [16]. Patients with renal cell cancer in the same study achieved PR or SD [17]. Due to these results and synergy apparent in xenograft models, it was decided to study CI-994 combined with gemcitabine in pancreatic cancer.

A phase I study was subsequently conducted to determine the MTD of CI-994 when given in combination with gemcitabine [18]. Patients received gemcitabine 1000 mg/m² i.v. on days 1, 8 and 15 of each 28-day cycle. Cohorts of three to six patients received 4, 6 or 8 mg/m² of CI-994 given daily for 21 days beginning on day 1 followed by 7 days of rest. The DLT of this combination was thrombocytopenia and the need to delay gemcitabine doses. The MTD of CI-994 given with gemcitabine was 8 mg/m²/day.

In light of the preclinical evidence of synergy of CI-994 with gemcitabine, plus evidence of antitumor activity in phase I and II trials, this phase II randomized trial of gemcitabine plus placebo versus gemcitabine with CI-994 in advanced pancreatic cancer was conducted. The primary end point of this trial was overall survival with secondary objectives including objective response, duration of response, time to treatment failure, change in quality of life (QoL) and pain response. Based on the phase I combination study, the dose of CI-994 used in the current clinical trial was 6 mg/m² on days 1–21 with gemcitabine 1000 mg/m² on days 1, 8 and 15 of each 28-day cycle.

**patients and methods**

**study design and entry criteria**

This was a randomized, double-blind, placebo-controlled, multicenter study of two treatment regimens. Eligible patients had to have a histological or cytologic diagnosis of advanced (stage II, III) or metastatic (stage IV) adenocarcinoma of the exocrine pancreas and not be considered a surgical candidate; a Karnofsky performance status (PS) of 70–100 determined within 2 weeks of randomization; expected survival ≥12 weeks; measurable or evaluable disease. No prior chemotherapy was allowed for advanced stage disease; however, prior 5-FU ± biological modulators such as leucovorin or interferon given as a radiation sensitizer was permitted if completed ≥3 months prior to randomization. Adequate renal, liver and bone marrow function determined within 2 weeks prior to randomization was also required.

The protocol and consent were reviewed by a central IRB and ethics committees with jurisdiction over the sites enrolling patients. All patients provided informed consent prior to registration.

Baseline evaluations at enrollment included disease measurements and confirmation of eligibility criteria. Eligible patients were then stratified based on prognostic factors [disease stage and PS (≤80%, >80%)] and randomly assigned to receive standard therapy [placebo + gemcitabine (PG)] or the experimental combination [CI-994 + gemcitabine (CG)]. Subsequent cycles of treatment were administered until progression, intolerable adverse events, or any other reason to discontinue treatment occurred. No crossover treatment occurred.

**therapy**

Gemcitabine was administered to both treatment groups (arms) as a 30-min infusion on days 1, 8 and 15 of each 28-day cycle at an initial dose of 1000 mg/m². In the PG arm, patients also took placebo capsules on days 1–21. In the CG arm, patients took CI-994 6 mg/m² orally once daily on days 1–21 of each 28-day cycle; doses were rounded using 2.5 mg, 5 mg and 10-mg capsules. Continuation of treatment in either arm was dependent on tolerance and hematological values. Dose modifications based on hematological toxicities occurred for gemcitabine and CI-994 (or placebo). Treatment courses with gemcitabine and CI-994 (or placebo) were stopped early if the patient had an absolute neutrophil count of <500/mm³, a platelet count <50,000/mm³, or a grade 3–4 treatment-related non-hematological toxicity. The dose of gemcitabine and CI-994 (or placebo) was reduced by 25% in subsequent cycles.

**evaluation of patients**

Response was investigator-assessed every 8 weeks during this study. A central radiology laboratory (RadPharm, Princeton, NJ) conducted an independent, blinded review of disease response by receiving second original copies of CT scans. Objective response in patients with measurable disease was defined as a ≥25% decrease in the sum of the products of measurable disease sites identified at baseline. Response was confirmed by another evaluation 24 weeks later. Tumor progression was defined as any bidimensional lesion with a ≥25% increase in the product of the perpendicular axis, the development of any new lesions, new ascites or new pleural effusions.

QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Core Cancer Module, the QLQ-C30 [19] and the disease-specific module for pancreatic cancer QLQ-PAN26 [20].

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Patients completed these modules at baseline and on day 1 of cycles 1–6, every third cycle and at the end of treatment. Each patient was assessed for pain intensity and analgesic consumption at baseline and then on days 1 and 15 of each cycle. Pain intensity was recorded on a scale of 0–10. Analgesic consumption was recorded by the patient for the coinciding 24-h period using an analgesic medication diary.

**study management and statistical analysis**
The study was conducted in parallel using identical protocols at 16 study centers in North America and 11 study centers in Europe. Patients enrolled in North America and Europe were combined for statistical analysis. A total of 172 patients (86 patients per arm) were needed to detect an improvement by 30% in median survival to 8 months, with a = 0.05 and 80% power, two-sided tests. Survival was calculated from the date of randomization until the date of death from any cause or last date of follow-up for surviving patients. TTP and survival were estimated using the method of Kaplan and Meier [21] and the log-rank test was used to test for statistical differences between the groups. Toxicity analyses were based on all patients who received one or more dose of study drug. SAS® (version 8.01) was used to run the analyses.

Parametric ANCOVA was used to test treatment arm differences in QoL change from baseline scores by scale at each timepoint. The ANCOVA was modeled to include the following terms: treatment, geographic location (North America, Europe), baseline KPS (≤80, >80), stage of disease (II/III, IV) and baseline QoL score. Differences in the rate of pain response were analyzed by the DMH test stratified by baseline KPS, disease stage and geographic location.

**results**

**patient characteristics**
Patient demographics and disease characteristics are summarized in Table 1. A total of 174 patients were randomized, 86 were assigned to the CG arm and 88 were assigned to the PG arm. Baseline characteristics in the two treatment arms were similar.

**duration of treatment and dose intensity**
Summary of treatment duration, dose reductions and dose intensity of both arms is summarized in Table 2. Overall, patients in the CG arm completed fewer cycles and required more dose reductions. Although the median duration of treatment between the two groups was similar, the CG arm received less study drug and gemcitabine compared with the PG patients. The ratio of total cycles completed to total cycles started was 214 of 360 (59%) for the CG arm and 291 of 394 (74%) for the PG arm. This difference in ratios was found to be significant (P < 0.0001) based on a post hoc chi-square test. The number of both study drug and CI-994/placebo dose reductions were greater in the CG arm relative to the PG arm. The mean percentage of gemcitabine received as planned was 67% for the CG patients and 89% for the PG patients. Decreased gemcitabine dose intensity in the CG arm was mainly secondary to myelosuppression.

**efficacy**
There was no observed difference in survival time between the CG arm and the PG arm. The placebo:CI-994 hazard ratio for survival was 0.980 (95% CI 0.701–1.370). The estimated median survival was 194 days in the CG arm and 214 days in the PG arm. The Kaplan–Meier plot of survival time is presented in Figure 1. Exploratory analysis revealed no differences between the experimental arm (CG) and the standard arm (PG) when evaluated for treatment location, performance status or stage.

Response and survival data are summarized in Table 3. Objective response rates based on the central radiologist’s assessment of bidimensional measurements were 1% in the CG arm and 6% in the PG arm. Response rates based on investigator assessments of bidimensional lesions were 12% in

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<sup>a</sup>Participants may have had more than one site of disease: two or less patients had metastasis to the adrenal glands, bone, kidney or skin.
the CG arm and 14% in the PG arm. No complete responses were noted by the central laboratory assessment in either arm. Time to treatment failure was similar in both treatment groups. Progressive disease was the most common reason that patients were withdrawn from study. Median time to treatment failure was 92 days in the CG arm and 103 days for the PG arm. The hazard ratio for PG was 0.837 (95% CI 0.596–1.175). Duration of response (as determined by the central radiology laboratory) for the one patient in the CG arm was 225 days. The median duration of response in the PG arm was 204 days (range 65–251).

Quality of life (QoL) questionnaires were completed at baseline for 97% of the CG patients and 90% in the PG arm. Baseline QoL scores were similar in both treatment arms. Due to a high patient discontinuation rate, approximately 60% of patients remained on study at the end of cycle 2. The majority of these patients (94% for CG and 92% for PG) completed QoL questionnaires at the end of cycle 2. Examination of the change from baseline to 2 months revealed a less positive, and in some cases negative, effect on QoL scores for CG compared with PG for the following scales and items of the EORTC QLQ-C30 and QLQ-PAN26 questionnaires: fatigue, appetite loss, social functioning, eating related items, pain, side-effects and ascites. There was at least a 10-point difference in favor of PG for each of these variables. With respect to pain assessments, 27.6% of CG patients and 24.6% of PG patients were considered responders, indicating a clinically significant decrease in pain.

Toxicity
Toxicities are summarized in Table 4. CG was associated with more grade 3–4 thrombocytopenia (25% versus 11%), anemia (13% versus 5%) and leukopenia (30% versus 16%) than PG. Non-hematological toxicities such as nausea, vomiting, anorexia and diarrhea were essentially identical with both treatments. Asthenia was the most commonly reported event and also appeared to be equal with both treatments. Death while on study occurred more frequently in the PG arm compared with the CG arm (24% versus 14%, respectively).

Discussion
Since the 1996 pivotal trial of Burris et al. [6], which established gemcitabine as the standard of care, minimal progress has been made in the treatment of pancreatic cancer. Many subsequent studies have attempted to improve the effectiveness of single agent gemcitabine, by using it as the basis for combination therapy. Several large phase III trials have been reported that compare single-agent gemcitabine with combinations of gemcitabine plus a traditional chemotherapeutic agent. Some of the drugs studied to date include 5-FU, irinotecan, cisplatin, exatecan, pemetrexed and oxaliplatin [22–27]. Two of the studies, with pemetrexed and oxaliplatin, produced statistically significant improved response rates; yet, despite the improvement in response, a secondary end point, the primary end point of overall survival was not met. The addition of oxaliplatin produced superior progression-free survival and clinical benefit. It is not clear if this possible improvement in efficacy is the result of the addition of oxaliplatin or due to the fixed dose rate infusion method of gemcitabine administration. Using a fixed dose rate appears superior to standard infusion in a randomized phase II trial [28].

Additional trials have utilized targeted therapy in combination with gemcitabine. Marimastat, a matrix metalloproteinase inhibitor [29], and Tipifarnib, a farnesyltransferase inhibitor [30], have both been combined with gemcitabine in large phase III trials. Unfortunately the median survival of these doublets was essentially identical to single-agent gemcitabine.

Until the recent study presented by Moore et al. [31], there has not been a study able to produce an increased survival benefit compared with single-agent gemcitabine. Moore’s study compared single agent gemcitabine versus gemcitabine plus the small molecular weight oral inhibitor of EGFR tyrosine kinase, erlotinib. The study randomized 569 patients to either single-agent gemcitabine versus gemcitabine plus erlotinib. A statistically significant improvement in overall survival was achieved in the gemcitabine + erlotinib arm (HR = 0.81).
The relative difference in median survival was relatively small, approximately 2 weeks. Improved 1-year survival was also seen with the combination, compared with single-agent gemcitabine, 17% and 24%, respectively. Progression-free survival was also improved (HR = 0.76). The experimental treatment was associated with more frequent grade 1 and 2 rash, diarrhea and hematological toxicities. This study achieved its primary objective with a unique molecule in combination with gemcitabine; however, it may not be universally accepted as the standard of care due to the relatively minimal difference in median survival, the toxicities associated with erlotinib, as well as the cost of this therapeutic modality.

The current study utilized a targeted oral agent, CI994, in combination with gemcitabine. CI994 inhibits histone deacetylase and is one of a new class of targeted anticancer agents [9]. This class of agents regulate chromatin structure and function through the removal of acetyl modifications from lysine residues of histones. This selectively alters the transcription of a relatively small numbers of specific genes, which then results in either decreased or increased rates of transcriptions. These agents have been found to be either additive or synergistic with a number of anticancer agents and radiation in inhibiting proliferation or inducing apoptosis in cultured tumor cell lines [32–34].

In this clinical trial, there were no observed trends in improved survival with the addition of CI994. Analysis of other efficacy parameters also failed to reveal any advantage favoring the experimental CG arm.

The response rate varied significantly between the treatment arms depending on whether the core laboratory or the investigator assessed response. The investigator assessment of response rates was consistently higher than the core laboratory. Response rate may not be a meaningful end point in the evaluation of efficacy in pancreatic cancer trials whether assessed by investigator or by core laboratory. Due to the extensive desmoplastic nature of these tumors, effective objective responses are difficult to evaluate.

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**Conclusion**

From this study, it is clear that CI994 in combination with gemcitabine does not appear to be as beneficial as single-agent gemcitabine for the treatment of pancreatic cancer. What remains to be answered is the effect of CI994 on the actual malignant cells. Was transcription of specific genes altered by this agent? If so, which genes showed epigenetic regulation by CI994? This information would seem critical for the understanding of these types of agents and their future
development. If transcriptional changes occurred, this specific gene expression alteration did not impair the growth of pancreatic cancers in this study. These specific alterations, however, could play an important role in other genetically different cancers. The ability to compare tumor samples pre- and post-treatment would help us to understand more fully these newer agents and hopefully lead to a more rational and more rapid development of effective anticancer therapy.

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references

25. O’Reilly EM, Aboou-Alfa GK, Lortet-Tieulent R et al. A randomized phase III trials of DX-8951f (Exatecan Mesylate: DX) and gemcitabine (GEM) vs. gemcitabine alone


