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CLINICAL TRIAL REPORT

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Pilot study of gemcitabine (10 mg/m^2 per min) and cisplatin

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Abstract *Purpose:* Gemcitabine and cisplatin are routinely used in combination. In this combination, gemcitabine at conventional doses of 1000–1500 mg/m^2 is delivered weekly as a 30-minute bolus. Laboratory data suggest that the synthesis of gemcitabine triphosphate is saturable, and that gemcitabine infused at a rate of 10 mg/m^2 per min optimizes accumulation of the triphosphate. Early clinical experience suggests that gemcitabine delivered by a more prolonged infusion is more myelosuppressive. In this pilot study, we wished to assess if full-dose gemcitabine when given with cisplatin could be delivered by this more prolonged infusion. *Methods:* In this study, all patients received cisplatin 75 mg/m^2. All gemcitabine doses were delivered at 10 mg/m^2 per min. For the initial cohort (level 1) the gemcitabine dose was 800 mg/m^2 per min. Subsequent escalations were 1000 mg/m^2 per min (level 2), and 1250 mg/m^2 per min (levels 3 and 4). For the first three cohorts, patients received gemcitabine on days 1, 8, and 15 and cisplatin on day 15 on a 28-day cycle. Patients on level 4 received gemcitabine on days 1 and 8 and cisplatin on day 8 on a 21-day cycle. Dose omissions or delays (holds) were mandated for NCI CTC grade 3 or 4 granulocytopenia or grade 2–4 thrombocytopenia. *Results:* Entered onto this dose-finding study were 23 patients (12 male, 11 female) with advanced solid tumors. Seven patients were treatment-naive. Six patients were treated on level 1, five each on levels 2 and 3 and seven on level 4. Patients received one to seven cycles of treatment. Myelosuppression-related dose holds occurred at all levels. First-cycle dose holds occurred in three of six, four of five, three of five and two of seven patients on successive levels. First-cycle grade 3 or 4 granulocytopenia/thrombocytopenia occurred in three patients on level 1, one patient on level 2, two patients on level 3 and three patients on level 4. There were no partial or complete responses. Four patients were removed for toxicity (three myelosuppression, one nephrotoxicity), one at physician discretion, and 15 with disease progression. Three patients stopped therapy with stable disease after 5–6 months. On level 3, three of five patients remained on therapy for 4 months or more, compared to only one patient on each of the other three levels. *Conclusions:* Weekly gemcitabine 1250 mg/m^2, utilizing a 10 mg/m^2 per min infusion rate, can be delivered with cisplatin 75 mg/m^2 with tolerable toxicity. When used in combination with cisplatin, however, the benefit of this fixed dose rate infusion gemcitabine compared to standard bolus gemcitabine remains to be determined.

Keywords Pilot study · Gemcitabine · Cisplatin · Combination therapy

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Introduction

Gemcitabine and cisplatin are clinically active in combination in a wide variety of tumor types [1, 2, 7, 8, 10, 11, 13]. As we learn more about the pharmacodynamics of gemcitabine, the optimal dose and scheduling of these two drugs in combination need to be assessed. Gemcitabine is phosphorylated to its triphosphate, dFdCTP, which is incorporated into DNA. The drug appears to

cause masked chain termination leading to inhibition of DNA synthesis [4]. Laboratory data derived from mononuclear cells demonstrate that the synthesis of the triphosphate is a saturable process that reaches a plateau at gemcitabine plasma concentrations above approximately 20 μM [3]. Bolus dosing of gemcitabine with higher peak concentrations may generate less dFdCTP accumulation than the same dose delivered by a protracted infusion. Confirmation of this hypothesis, by assaying dFdCTP in clinical solid tumor samples in different treatment schedules, is difficult due to the technical challenges.

Given the potential advantage of the fixed dose rate 10 mg/m^2 per min infusion of gemcitabine, and the demonstration of clinical activity of gemcitabine in combination with cisplatin, our goal was to assess if full-dose gemcitabine could be used when gemcitabine administration was extended using a rate of 10 mg/m^2 per min. For this pilot study, we chose a schedule utilizing cisplatin given once per cycle on the last day of each treatment in order to permit maximum gemcitabine delivery. Gemcitabine was started at a lower dose than that commonly used, anticipating some increased myelosuppression from the longer infusion, with a planned escalation into a more commonly used dose range. Both the common 4-week cycle and a 3-week cycle were assessed.

Methods and materials

Eligibility criteria for patients entering this study, which was conducted at Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Cancer Institute of New Jersey/University of Medicine and Dentistry of New Jersey, included: histologically proven metastatic or recurrent nonhematologic malignancy; lack of a standard therapy or progression on such treatment; measurable or evaluable disease; performance status of 0–2 (ECOG); estimated survival ≥8 weeks; absence of severe concurrent medical problems which might cause an interruption in therapy; no prior therapy with gemcitabine or cisplatin; completion of any prior radiotherapy or chemotherapy at least 4 weeks prior to entry onto trial; adequate renal, hepatic and hematologic function as judged by creatinine ≤ 1.5 mg/dl, creatinine clearance ≥60 ml/min, bilirubin ≤ 1.5 mg/dl, SGOT not more than five times the upper limit of normal, neutrophils > 2000/mm^3, platelets ≥100,000/mm^3; and signed informed consent.

All patients in the first three cohorts received gemcitabine at the assigned dose level weekly on days 1, 8 and 15 on a 28-day cycle. On dose level 4, patients received gemcitabine on days 1 and 8 on a 21-day cycle. All gemcitabine was delivered at 10 mg/m^2 per min in 250 ml normal saline. Cisplatin at 75 mg/m^2 was administered in a minimum of 500 ml normal saline over 2 h starting immediately after completion of the gemcitabine. Gemcitabine was escalated from 800 mg/m^2 on level 1 to 1000 mg/m^2 on level 2 and to 1250 mg/m^2 on levels 3 and 4.

A new cycle could be initiated if patients had neutrophils ≥1500/mm^3 and platelets ≥100,000/mm^3 and had recovered from all nonhematologic toxicity of grade 1 or more. Cisplatin could only be given if serum creatinine was ≤ 1.5 mg/dl and real or calculated clearance was ≥60 ml/min. Treatments within a cycle were delivered only if neutrophils were ≥1000/mm^3 and platelets ≥75,000/mm^3 and no grade 3 or 4 toxicities were present. Day 8 treatment for the first three levels was omitted if the above criteria were not met. Cisplatin treatments (day 15 for the first three levels and day 8 for the final level) could be delayed for up to 1 week so that the above criteria could be satisfied. There was always a 14-day rest before initiation of the next cycle.

Toxicity was assessed by the NCI Common Toxicity Criteria (version 1.0). Dose-limiting toxicity (DLT) was determined during cycle one of treatment and consisted of grade 3 or 4 nonhematologic toxicities (excluding nausea/vomiting), grade 4 hematologic toxicity lasting ≥5 days occurring during treatment or within 1 week of treatment completion, or dose omission or delay for toxicity of 1 week in a cycle, or delay in initiation of a cycle beyond the mandated 2 weeks because of toxicity.

Three patients were to be entered at each level. If only grade 1 or lower toxicity was noted and no doses were omitted, the next cohort level was to be initiated. If any patient developed grade 2 or more nonhematologic toxicity except weight loss or required an omission of a dose, a total of five patients would be treated at that level. If, among five patients in the expanded cohort, DLT was noted in only one patient, the dose level escalation would continue. If two patients had DLTs at a given dose, that dose was considered the maximum tolerated dose (MTD). In the course of the study, it became clear that dose delays due to mild myelosuppression or at physician discretion were frequent and did not represent clinically significant toxicity. Therefore, the protocol was amended to allow two dose delays per cycle prior to the designation of DLT. To facilitate protocol accrual in both institutions, the protocol was amended to allow five to seven patients per level. Escalation of the gemcitabine dose was stopped at 1250 mg/m^2 over 125 min, a dose at or above that commonly used in combination studies of 30-min infusion gemcitabine with cisplatin [1, 2, 8, 10, 11, 13].

Patients were removed from study for disease progression, treatment delay beyond 2 weeks, grade 3 or 4 nonhematologic toxicity excluding nausea/vomiting, grade 3 or 4 hematologic toxicity lasting more than 7 days, physician discretion, or patient request.

Response was assessed at the end of two cycles and then every two cycles thereafter. Documentation of response required two assessments, at least 1 month apart, documenting and confirming the response. A complete response consisted of disappearance of all measurable and evaluable disease with normalization of any elevated tumor markers. A partial response consisted of a decrease of 50% or more in the sum of the products of the perpendicular diameters of all measurable lesions with no development of new lesions. Progression consisted of a 50% increase in the sum of the products of all measurable lesions over the smallest sum observed (or baseline, if no decrease), or worsening of evaluable disease or appearance of new lesions. Stable disease was that which did not qualify as a complete or partial response, or as progression.

Results

Entered into the study were 23 eligible patients (12 men and 11 women) with advanced solid tumors. Their median age was 61 years (range 41–80 years). The median performance status was 0 (range 0–2). Of the 23 patients, 7 were chemonaive, and 12 had had prior chemotherapy and 4 chemoradiotherapy. Tumor types included: pancreas (eight), cholangiocarcinoma (two), gastric (two), colon (three), bladder (two), and prostate, hepatocellular, small bowel, anal, lung and peritoneal (one each). Of the 23 patients, 16 received treatment on the 28-day cycle, six on level 1 (gemcitabine 800 mg/m^2 per min), five on level 2 (gemcitabine 1000 mg/m^2 per min) and five on level 3 (gemcitabine 1250 mg/m^2), and 7 received treatment on the 21-day cycle on level 4 (gemcitabine 1250 mg/m^2 per min).

The median number of treatment cycles was two (range one to seven). Three patients received only the

first cycle, all on level 4. One was removed from study for progression, one for renal toxicity and one with persistent myelosuppression. Two patients remained on study for six cycles and, a third for seven.

All 23 patients were evaluable for toxicity. Myelosuppression was the predominant toxicity (Table 1). Grade 3 or 4 neutropenia occurred in one or more patients in each cohort and did not increase in frequency with increasing gemcitabine dose in this small group of patients. Grade 3 or 4 thrombocytopenia was noted sporadically in one or more patients on levels 2–4, but again did not seem more severe with higher gemcitabine doses. The briefer 21-day cycle of gemcitabine days 1 and 8 and cisplatin day 8 (level 4) surprisingly yielded the lowest platelet nadirs in the first cycle. Only two chemonaive patients were treated in this cohort.

Doses were delayed or not given if patients had persistent toxicity, as noted above. Myelosuppression-related dose holds in the first two cycles occurred in three of six, four of five, three of seven and two of seven patients at successive levels. Other grade 3 or 4 toxicities were rare and not unexpected. Grade 3 anemia was documented in three patients, grade 3 nausea/emesis in three patients, and grade 3 hyponatremia in one patient. A single patient was removed from study because of a rise in creatinine to 2.7 mg/dl, which did not return to baseline. Less severe toxicities included lesser grades of nausea, emesis, constipation, depression, and fatigue. One patient with pancreatic cancer developed a deep vein thrombosis. A patient with metastatic lung cancer developed grade 3 dyspnea at the time of progression. It is likely that the events in these last two patients were related to their underlying malignancies. A patient with pancreatic cancer suffered a myocardial infarction during the first cycle, but subsequently received five cycles of therapy with stable disease.

Criteria for the MTD, as defined by two DLTs at a given level during the first cycle of therapy, were technically met at level 4 as protracted myelosuppression in one patient and nephrotoxicity in a second. In this final cohort, three patients received only one cycle; the remaining four patients received between two and four cycles. Patients on level 4 were removed from trial for progression (four), myelosuppression (two) and renal dysfunction (one). Patient tolerance was better on level 3, wherein all five patients received at least two cycles, and three patients received four or more cycles. No patient at this level was removed from study because of toxicity.

Of the 23 patients, 21 were evaluable for response including one patient who progressed in cycle 1. There were no complete or partial responses. Three patients maintained stable disease and stopped after 5–9 months of therapy. On level 3, three of five patients remained on therapy for 4 months or more, compared to only one patient each on the three other dose levels. Of the eight patients with pancreatic cancer, stable disease of 4 months or greater was noted in four patients. Four patients were removed from the trial for toxicity, three with persistent myelosuppression and one with nephrotoxicity. One patient with clinically stable metastatic bladder cancer and intercurrent cellulitis was removed at physician discretion during the second cycle, and 15 were removed with disease progression.

Discussion

Gemcitabine has been in clinical use for a decade, yet optimum dosing is still controversial. In a randomized phase II study in patients with pancreatic cancer, patients were randomized either to gemcitabine 2200 mg/m^2 over 30 min or gemcitabine 1500 mg/m^2 over 150 min, receiving drug weekly for 3 weeks every 28 days [12]. Preliminary results suggest a longer median survival with infusion at the fixed dose rate of 10 mg/m^2 per min than with the standard 30-min infusion (M. Tempero, unpublished observations). If fixed dose rate infusion proves significantly more efficacious in this pancreatic trial, extrapolation to the routine use of fixed dose rate infusion for other tumors or when gemcitabine is used in combination chemotherapy should be considered carefully.

Our findings demonstrate that the schedules of gemcitabine 1250 mg/m^2 over 125 min on days 1, 8 and 15 with cisplatin 75 mg/m^2 day 15 every 28 days (level 3) or on days 1 and 8 with cisplatin on day 8 every 21 days (level 4) were tolerable, with toxicity not very different from the more common 30-min infusion. More patients were able to remain on level 3 treatment longer, possibly suggesting this to be the better tolerated therapy. There were no responses in our study although three patients stopped therapy with stable disease after 5–9 months of therapy.

Table 1. Grade 3/4 granulocyte-platelet toxicity and dose omission

Level	Patients	Course 1					Course 2				
		Neutropenia		Thrombocytopenia		Doses delivered (%)	Neutropenia		Thrombocytopenia		Doses delivered (%)
		Grade 3	Grade 4	Grade 3	Grade 4		Grade 3	Grade 4	Grade 3	Grade 4	
1	6	2	1	–	–	83	3	–	–	–	83
2	5	–	–	–	1	73	1	–	1	–	75
3	5	2	–	–	–	80	1	1	2	–	73
4	7	3	–	1	1	79	–	1	2	–	100

Studies of gemcitabine at 10 mg/m^2 per min in combination with cisplatin should continue. Given our very limited goals, we did not address the multiple different schedules that have been suggested, such as weekly cisplatin in combination with weekly gemcitabine, or cisplatin given the first week of each cycle rather than the last, or administering cisplatin 24 h before or after gemcitabine [5, 6, 9]. These other issues remain to be addressed.

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