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Phase I study of gemcitabine, docetaxel and imatinib in refractory and relapsed solid tumors

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Summary

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Purpose—In a phase I study, the combination of gemcitabine and imatinib was well tolerated with broad anticancer activity. This phase I trial evaluated the triplet of docetaxel, gemcitabine and imatinib.

Experimental Design—Imatinib was administered at 400 mg daily on days 1–5, 8–12 and 15–19. Gemcitabine was started at 600 mg/m^2 at a rate of 10 mg/min on days 3 and 10 and docetaxel at 30 mg/m^2 on day 10, on a 21-day cycle. Diffusion and dynamic contrast-enhanced perfusion MRI was performed in selected patients.

Results—Twenty patients with relapsed/ refractory solid tumors were enrolled in this IRB-approved study. The mean age was 64, and mean ECOG PS was 1. Two patients were evaluated by diffusion/perfusion MRI. After two grade 3 hematological toxicities at dose level 1, the protocol was amended to reduce the dose of imatinib. MTDs were 600 mg/ m^2 on days 3 and 10 for gemcitabine, 30 mg/ m^2 on day 10 for docetaxel, and 400 mg daily on days 1–5 and 8–12 for imatinib. Dose limiting toxicities after one cycle were neutropenic fever, and pleural and pericardial effusions. The best response achieved was stable disease, for six cycles, in one patient each with mesothelioma and non small cell lung cancer (NSCLC) at the MTD. Two patients with NSCLC had stable disease for four cycles.

Discussion—An unexpectedly low MTD for this triplet was identified. Our results suggest drug-drug interactions that amplify toxicities with little evidence of improved tumor control.

Keywords

Phase I Gemcitabine; Docetaxel and Imatinib; Diffusion and dynamic contrast-enhanced perfusion MRI

Introduction

Gemcitabine (GEM), docetaxel and imatinib are all active anticancer agents. In particular, imatinib has altered treatment of chronic myeloid leukemia (CML), gastrointestinal stromal tumor (GIST) and hypereosinophilic syndrome because of its inhibition of the BCR-ABL tyrosine kinase (TK), as well as the TK receptors for platelet-derived growth factor (PDGF), and *c-kit* [1–4]. Gemcitabine and docetaxel are used as single agents and in combination to treat wide variety of cancers including pancreatic cancer [5], non small cell lung cancer [6–9], metastatic breast cancer [10–13], ovarian cancer [14], and urothelial cancer [15]. The combination of gemcitabine and docetaxel at different dosing schedules has shown activity in multiple different malignancies including lung cancer, sarcoma, and breast cancer [16–19].

Combining TK inhibitors with cytotoxic chemotherapy may yield additional benefit as compared to cytotoxics alone. Pietras and colleagues have suggested that inhibition of the PDGFR signal transduction pathway with imatinib may decrease interstitial hypertension within the tumor stroma and allow for improved uptake of systemic therapy within the tumor [20]. Thus, combining the PDGFR inhibition of imatinib with chemotherapy may enhance tumor uptake of anticancer-therapy.

A Phase I trial of gemcitabine and imatinib mesylate for the treatment of patients with refractory solid tumor malignancy has shown substantial activity in solid tumors with little increase in toxicities [21]. Daily imatinib with low dose gemcitabine was prohibitively toxic [21]. However, the administration of gemcitabine with imatinib "bracketing" was more successful. Among 54 patients treated with gemcitabine on days 3 and 10, in combination with imatinib, given on days 1–5, 8–12, and 15–19, three patients had partial responses (laryngeal, renal, mesothelioma) and seventeen patients had stable disease for 6 months or longer. The maximum tolerated dose (MTD) and the proposed dose for phase II usage, was gemcitabine 1500 mg/m^2/150 min and imatinib 400 mg/day on days 1–5, 8–12, and 15–19. For the combination of docetaxel and imatinib, an MTD of docetaxel 30 mg/m^2 weekly with imatinib 600 mg daily has been reported [22].

Since gemcitabine and docetaxel are active in combination and gemcitabine and imatinib are as effective and well tolerated in combination, the triplet combination of gemcitabine, docetaxel and imatinib mesylate appeared promising and worthy of further investigation.

Therefore, we conducted an open label, dose escalation study of gemcitabine and docetaxel in combination with fixed dose imatinib mesylate in patients with refractory malignancies with the purpose of identifying the maximum tolerated dose of each component in the triple regimen. Based on the prior phase I study of gemcitabine/imatinib combination, the "bracketing" imatinib schedule was used. The study was conducted at the Cancer Institute of New Jersey and the University of Michigan.

As part of the study, dynamic contrast-enhanced (DCE) perfusion and diffusion magnetic resonance imaging was performed on a limited number of patients as a correlative study. Diffusion imaging has been shown to be an earlier predictor of response to therapy in patients with brain gliomas. In this study, we examined the applicability of this technique in other tumors and investigated, in a preliminary fashion, whether treatment-induced perfusion changes could be detected and whether they were predictive of response.

Patients and methods

Adult patients with refractory solid tumor malignancies with the following eligibility criteria were included in this study: ECOG performance status 0–2, estimated survival >3 months, measurable or evaluable disease, intact GI absorption; total leukocytes>3500/μl; neutrophil count>1,500/μl; platelet count > 125,000/μl; prothrombin time and partial prothromboplatin time within institutional upper normal limits (ULN), serum creatinine<1.5 mg/dl, total bilirubin<1.5 mg/dl; ALT, AST and alkaline phosphatase<2.5x the institutional ULN. Patients were also required to have had their last chemotherapy or radiotherapy at least 4 weeks prior to start of the trial and to have recovered from the toxicities of previous chemotherapy or radiotherapy. Prior therapy with gemcitabine and/or docetaxel was allowed.

Patients were excluded if they had more than 12 months of continuous cytotoxic therapy; more than 2 prior cytotoxic regimens for metastatic disease; history of bone marrow transplantation; radiation to more than 25% of bone marrow; known or suspected bone marrow infiltration by cancer; newly diagnosed or uncontrolled brain metastasis; chronic

uncontrolled diarrhea and/or daily emesis; Grade 2 or higher neuropathy; or significant peripheral edema. Patients were instructed to not use acetaminophen or grapefruit juice during the trial.

The protocol was approved by the IRBs at the Cancer Institute of New Jersey and the University of Michigan.

All dose level cohorts consisted of at least three patients. No intra-patient dose escalation was allowed. Dose escalation could not occur until at least three patients had completed one cycle at the active dose level and were evaluable for toxicity. However, patients were added into a cohort to replace patients who, for reasons other than toxicity, did not receive a full cycle of all drugs.

If none of the first three patients in any cohort experienced dose-limiting toxicity (DLT), the next three patients were enrolled at the next higher dose level. If one of the first three patients in a dosing cohort had a DLT, two more patients were treated at that dose level. If neither of those additional patients had a DLT, the dose was escalated. If one of these additional patients had a DLT, the dose was considered as the MTD. If two of five patients at a given dose level had a DLT, two more patients were treated at the prior dose level (if only three patients were previously treated at that prior dose) to confirm tolerability.

DLT was defined as the occurrence of any of the following serious adverse events during the first cycle of therapy: grade 3–4 non-hematologic toxicity (including nausea and vomiting that could not be controlled with oral medication); grade 4 hematologic toxicity that occurred during treatment or within 1 week of treatment completion and lasted >7 days; omission or delay of treatment for toxicity by two or more doses in a cycle; or, delay in initiation of a treatment cycle beyond 2 weeks.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. All patients receiving one dose of protocol therapy were evaluable for toxicity.

Pretreatment evaluations

Baseline evaluations included history, complete physical examination, ECOG performance status, CBC with platelet count, serum chemistries and electrolytes, chest x-ray, EKG, tumor markers, if indicated. In addition to these evaluations, imaging studies (computed tomography or magnetic resonance imaging) of the sites of measurable disease were performed.

Treatment schema

Cycles were repeated every 21 days. Imatinib mesylate was taken orally at 400 mg per day on days 1–5, 8–12, and 15–19, preferably with a meal. Gemcitabine was administered as a 10 mg/m^2/min infusion, starting at 600 mg/m^2 on days 3 and 10. Docetaxel was administered as a 60-min infusion starting at 30 mg/m^2 on day 10. Premedications for docetaxel included dexamethasone 8 mg orally twice daily on the day prior to chemotherapy, on the day of chemotherapy and on the day after chemotherapy. After two cycles of

docetaxel without hypersensitivity reaction, the dexamethasone schedule could be modified at the discretion of the treating physician.

Patients were assessed for toxicity weekly and for disease regression or progression every two cycles. All patients receiving any treatment were considered evaluable for response. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [23].

Treatment at the second dose level was associated with unexpected myelosuppression. This was attributed to possible imatinib toxicity due to Days 15–19 of imatinib, and the protocol was amended to include dosage levels 2A, 2B as shown in Table 1. Cohort 2B was designed with increasing gemcitabine but fixed docetaxel dose to determine whether the toxicities were dependent on the other two drugs.

Diffusion and perfusion magnetic resonance imaging (MRI)

Diffusion-weighted images (DWI) of one primary or metastatic lesion were acquired on a 3T human MRI system (Philips Medical Systems, Best, The Netherlands) using a 6-channel torso array coil. DWI was performed using a single-shot echoplanar imaging technique with parallel imaging (SENSE=2), an 200×172 acquisition matrix over a 350×300 mm field-of-view (FOV), and 5 mm axial slices. Three-axis diffusion sensitization at b-values 0 and 800 s/mm^2 were acquired with fat suppression and 8 averages, TR/TE=3200/60 ms. Apparent diffusion coefficient (ADC) maps were compared to pre-therapy maps by inspection on a quantitative color scale display, and by region of interest analysis. Dynamic contrast-enhanced (DCE) perfusion sensitive MRI was performed using 3D T1-weighted fast field echo (3D T1-FFE) sequence at 20 s temporal resolution during injection of a body-weight dose of gadolinium contrast material (Magnevist at 0.1 mMol/kg). DCE acquisition parameters included: 364× 240×70 axial slices at 1×1×2mm acquired resolution; SENSE=2; TR/TE/Flip=4.6/2.2 ms/12°. The Ktrans maps were derived from the DCE image series using established Tofts 2-compartment model for contrast exchange.

Included participants signed informed consent for this portion of the protocol, did not require sedation for an MRI, did not have metal fragments within their body that might put them at increased risk for harm from the MRI, and were treated at the University of Michigan. MRIs were performed prior to therapy, on cycle 1, day 10 prior to infusion, and on cycle 2, day 3.

Results

Between February 2006 and January 2008, 20 patients were enrolled into the study. Patient characteristics are listed in Table 2.

Of the first six patients, two patients had a delay in day 10 dosing. One patient at drug level 2 had day 10 dose held; at drug level 2A, day 10 doses were held for two patients. At least six patients had delays in second cycle initiation due to toxicities. The dose limiting toxicities are reported in Table 3.

The MTD was determined to be 600 mg/m^2 for gemcitabine, 30 mg/m^2 for docetaxel, and 400 mg per day given on days 1–5 and 8–12 for imatinib. The dose limiting toxicities were neutropenic fever, and pleural and pericardial effusions. The best response achieved was stable disease, for six cycles, in one patient each with mesothelioma and non small cell lung cancer (NSCLC) at the MTD. Two other patients with NSCLC had stable disease for four cycles.

For all patients, the median number of cycles received was 2; and the median duration of therapy was 12 weeks with a range from 4 to 30 weeks.

Functional MRI was performed on two patients. Changes in the perfusion and diffusion weighted images were demonstrated in both patients. Figure 1 shows minimal changes in K_{trans} (microvascular permeability) indicating decreased perfusion at the middle of cycle 1 and increased perfusion at the initiation of cycle 2 in a patient with a uterine leiomyosarcoma. The clinical significance of these changes is unclear. Figure 2 illustrates changes in the tumor ADC or water mobility on diffusion MRI sequences in the same patient. Increased ADC has been shown to correlate with patient benefit from therapy in other malignancies.

Discussion

This phase I study of docetaxel, gemcitabine, and imatinib yielded an unexpectedly low maximally tolerated dose for the combination of these drugs. The results are surprising, given that, in combination with bracketing imatinib, gemcitabine could be given at much higher doses (up to 1500 mg/m^2 over 150 min) in our previous phase I study [21].

The potential causes for the higher toxicities observed in the current study include patient factors and possible drug interactions. Since this three drug combination has not been studied before, we reviewed experiences with each of the 2-drug combinations to determine possible etiological factors for these significant toxicities.

Host factors

Compared to the prior study of gemcitabine and imatinib, this patient population was comparable in terms of demographics (age, sex, performance status), specific diagnoses and number of prior therapies (45% of patients had more than two prior chemotherapies in this study vs. 41% in the gemcitabineimatinib study) [21]. In the present study, more patients had prior radiotherapy (60% v. 33%). Thus, a higher proportion of patients in this study had less bone marrow reserve.

In a previous phase I study of gemcitabine and docetaxel, the MTD was determined at 800 mg/m^2 on days 1 and 8 for gemcitabine, and 40 mg/m^3 on days 1 and 8 every 21 days for docetaxel, a regimen not too dissimilar from the one used in the present study [24]. The dose limiting toxicities were Grade 3/4 neutropenia in 62% of patients (8/13) who had received two or more prior chemotherapy regimens. However, no neutropenia was noted among fifteen patients who had received no more than one prior chemotherapy regimen [24]. In our study, among the patients who experienced neutropenic fever, two patients in Level 2 had

received 2 prior therapies and two patients in level 2A had received 0 and 3 prior chemotherapies, respectively.

Thus, the number of prior therapies, including radiation therapy, may have played a role in the low MTD of the present study. Many studies of gemcitabine and docetaxel use filgrastim or pegfilgrastim routinely. This protocol did not utilize growth factors, likely contributing to higher rates of neutropenia and related toxicities.

Drug-drug interactions

Gemcitabine and docetaxel combination has been studied much more extensively than the combination of imatinib with gemcitabine or imatinib with docetaxel. Gemcitabine and docetaxel combination has been studied in different schedules including weekly gemcitabine for 3 weeks out of four with various dosing of docetaxel [25, 26]; gemcitabine on days 1 and 8 with docetaxel on day 8 [27–29] every 21 days, and gemcitabine and docetaxel on days 1 and 8 every 3 weeks.

In studies with similar schedule of gemcitabine and docetaxel, a broad range of dosages was tolerated (Table 4). There are several studies where toxicities were observed at lower dosages for each of the two drugs. In one phase I study, gemcitabine and docetaxel were safely administered weekly for three out of 4 weeks. The MTD for gemcitabine was 750 mg/m2 and docetaxel 35 mg/m^2, and the dose-limiting toxicity (DLT) was neutropenia [30]. It has been suggested that specific sequencing of the drugs (docetaxel followed by gemcitabine) produces powerful cytocidal effect [31]. It is hypothesized that the gemcitabine attacks cells as they progress to the S phase after recovering rapidly from an M phase block induced by docetaxel [31]. In our study, the gemcitabine preceded docetaxel.

The addition of imatinib may have amplified the toxicities of gemcitabine in our patients. Though we did not see severe hematological toxicities in our previous study of gemcitabine and imatinib, neutropenia was noted on day 10 in the current study, even before docetaxel administration. The combination of chemotherapy with imatinib may be problematic, and may be worse in patients with prior radiotherapy. In other Phase I studies of imatinib with gemcitabine or doxorubicin, the initial dose levels produced DLT when imatinib was given daily with chemotherapy [32].

It has been hypothesized that inhibition of PDGFR may decrease tumor interstitial fluid pressure, allowing better penetration of chemotherapeutic drugs. A mouse xenograft study showed increased gemcitabine efficacy when administered with imatinib, an outcome postulated as due to increased gemcitabine delivery [33]. Perfusion MRI to evaluate for possible increased tumoral uptake of chemotherapy after imatinib administration was designed as part of the present study. Unfortunately, due to the limited number of patients evaluated with functional MRI, no conclusions could be drawn from this analysis. One might hypothesize that increased uptake of gemcitabine was seen less in tumor cells and more in normal hematopoietic cells as was reflected in the increased hematologic toxicity without any change in efficacy.

There is no noted pK interaction between imatinib and docetaxel [34]. Our previous study did not show any effect of imatinib on gemcitabine pK [21]. Because of this, no formal pK evaluations were performed as part of this trial, a limitation of the study.

Pleural and pericardial effusions, among the dose limiting toxicities observed, are generally rare with gemcitabine and docetaxel, but can be associated with imatinib [35–37]. One patient each had pericardial effusion and pleural effusion during cycle #1, which is likely related to imatinib. The role of docetaxel and gemcitabine in those cases was unclear.

Conclusion

In this combination the maximally tolerated dose was: imatinib 400 mg orally per day on days 1–5 and 8–12, gemcitabine 600 mg/m^2 in FDR infusion over 60 min on days 3 and 10, and docetaxel 40 mg/m^2 on day 10. The combination was unexpectedly toxic without any apparent increase in efficacy in this limited patient population. Further studies involving imatinib in combination with cytotoxic chemotherapy should be performed with caution and close monitoring of toxicities. Perfusion and diffusion MRI is feasible in this population of patients and further studies should be performed to determine the utility of this technique.

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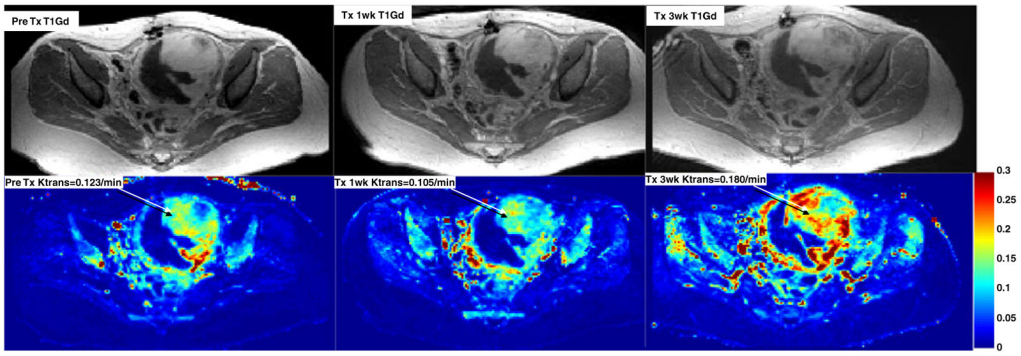

Fig. 1.

MRI imaging with conventional (*top row*) and perfusion (*bottom row*) sequences in a patient with uterine leiomyosarcoma showing variable microvascular permeability (Ktrans) at baseline (*left*), cycle 1 day 10 (*middle*), and on cycle 2 day 3 (*right*) of therapy

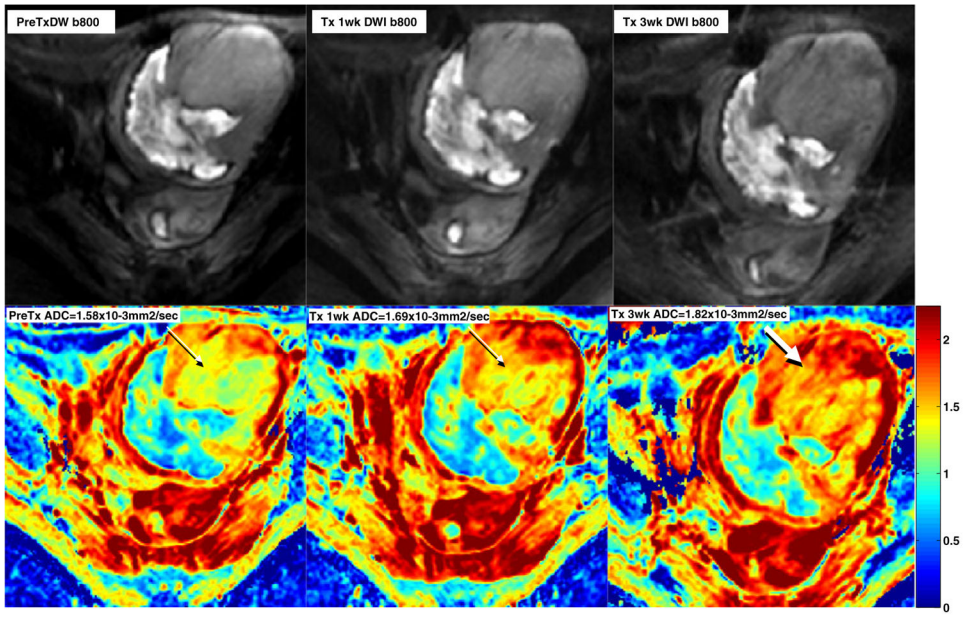

Fig. 2.

MRI images in the same patient with uterine leiomyosarcoma showing conventional (*top row*) and diffusion sequences (*bottom row*) prior to(*left*), on cycle 1 day 10 (*middle*), and on cycle 2 day 3 (*right*) of therapy. Images reveal an increase in diffusion (ADC or water mobility) as therapy progresses

Table 1

Dosing levels

Regimen	Gemcitabine 10mg/m^2/min on Days 3, 10	Docetaxel IV 60min infusion on Day 10	Imatinib Mesylate (mg) on Days 1–5, 8–12	# patients
1*	600 mg/m^2	30 mg/m^2	400 mg (included days 15–19)	8
2	600 mg/m^2	45 mg/m^2	400 mg (included days 15–19)	4
2A	600 mg/m^2	45 mg/m^2	400 mg	5
2B	600 mg/m^2	30 mg/m^2	400 mg	2

Table 2

Patient characteristics

	No. of patients
Total	20
Median age, years (range)	64.5(43–83)
Sex	
Male	12
Female	8
Performance status, ECOG	
0–1	16
2	4
Tumor type	
Lung Cancer	
NSCLC	4
SCLC	1
Sarcoma	5
Pancreatic/Biliary	3
Mesothelioma	2
Bladder	2
Other (colon, Breast, Cervical, Melanoma)	4
No. of prior chemotherapy regimens	
0	4
1	7
≥ 2	9
Prior Radiotherapy	12

Table 3

Dose limiting toxicities

Dose level	# patients	DLT
1*	8	2 Neutropenic Fever
2	4	2 Neutropenic Fever
2A	5	2 Neutropenic Fever and Weakness
2B	2	1 Neutropenic Fever

Table 4

Combination of Gemcitabine and Docetaxel

Study	Phase	Disease	Gemcitabine dose (mg/ m^2) Days 1,8	Docetaxel dose (mg/ m^2) on Day 8	Cycle duration	Commen
Matsui [38]	I/II	NSCLC	1000 mg/m^2	50 mg/m^2	21	
Hensley [39]	II	Uterine Leiomyosarcoma	900 FDR mg/m^2	100 mg/m^2	21	• Neutropenia 12% grade 4, 5% Grade 3 • Anemia 24% grade 3 • Thrombocytopenia grade 3 in 9.5%, grade 4 in 5% • GCSF administered
Georgoulilas [40]	III	NSCLC	1100 mg/m^2	75 mg/m^2	21	
Ebeling [41]	Retrosp	STS	900 mg/m^2	100 mg/m^2	21	• 47% grade 3 or 4 hematological toxicity • 26% grade 3 or 4 nonhematological toxicity
Boukovinas [42]	II	elderly NSCLC	1100 mg/m^2	100 mg/m^2	21	• GCSF administered • Neutropenia 18.2% Grade 3–4 • Febrile neutropenia in 3.9% patients
Labourey [43]	II	HNC	1000 mg/m^2	75 mg/m^2	21	• Neutropenia Grade 3 or 4 in 45% (18 patients). • Three treatment-related deaths (7.5%) due to infection were reported.
Maki [44]	II	STS	900 mg/m^2 FDR	100 mg/m^2	21	• GCSF administered