Potential Role of Platelet-Derived Growth Factor Receptor Inhibition Using Imatinib in Combination with Docetaxel in the Treatment of Recurrent Non-small Cell Lung Cancer

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Introduction: Platelet-derived growth factor receptor (PDGFR) is expressed in lung cancer and is involved in angiogenesis. Preclinical models demonstrated that imatinib (Im) regulates angiogenesis through PDGFR inhibition and enhances efficacy of chemotherapy. Hypothesis: We hypothesized that Im plus docetaxel (D) would have a synergistic effect detectable by an increase in response rate in patients with recurrent non-small cell lung cancer (NSCLC).

Methods: A phase II trial to evaluate Im in combination with D in patients with recurrent NSCLC was conducted. The primary end point was response rate, using a Simon two-stage design. Eligible patients had measurable disease and no more than two chemotherapy regimens. D was given at 30 mg/m^2/wk intravenously $\times$3 every 4 weeks and oral Im at 600 mg daily for four cycles. Patients required two cycles to be evaluable for response. Nonprogressors after four cycles continued with Im maintenance until progression or for a total of 12 months.

Results: Twenty-three patients were enrolled in the first stage. Toxicity was mainly nonhematologic. We observed one partial response (5.5%), four stable disease (22.2%), and 13 progressed (72.2%). Median time to progression was 1.9 months, and median overall survival was 6.1 months. Two patients who went on Im maintenance had time to progression of 7.78 months and 15.8 months.

Conclusion: Im in combination with D did not achieve its primary objective of improving response rate in patients with recurrent NSCLC. An increased understanding of the complex PDGFR pathway in lung cancer and alternative strategies to inhibit it are needed.

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Advanced non-small cell lung cancer (NSCLC) is nearly always fatal. First-line therapy using platinum doublets demonstrated a time of progression of only 3 to 4 months and 30% 1-year survival rate.[1] The use of second-line treatment after failure of a platinum-based doublet has become routine for patients with advanced NSCLC, producing a modest increase in survival. Docetaxel (D), the first agent approved for patients with relapsed NSCLC with good performance status (PS), showed an improved median survival and quality of life compared with best supportive care.[2] Compared with ifosfamide or vinorelbine, it showed a superior response rate, 1-year survival rate, and a progression-free survival (PFS) of 26 weeks.[3] Nevertheless, this benefit was incremental with a response rate of 7 to 8% and median survival times of 6 to 7 months. Clearly, there is a need to develop more active treatment in both the first and second-line setting to further improve survival of these patients.

A novel targeted pathway involves platelet-derived growth factors (PDGFs) that comprised four polypeptide chains (PDGF-A, B, C, and D) encoded by four different genes that result in five dimeric isoforms (PDGF-AA, -BB, -CC, -DD, and -AB). These isoforms bind to one of three PDGF receptors (PDGFR-$\alpha\alpha$, PDGFR-$\beta\beta$, or PDGFR-$\alpha\beta$) resulting in the activation of a downstream signaling cascade that promotes cellular proliferation, migration, and survival.[4] The PDGF pathway is also involved in angiogenesis by inducing vascular endothelial growth factor (VEGF),[5] recruiting pericytes, and stimulating vascular smooth muscle cells.[6] The four PDGF chains also contain a domain similar to VEGF, named the PDGF/VEGF homology domain.[7]

Both PDGF and its receptor (PDGFR) have been detected in lung cancer cells but not in normal cells. PDGF is expressed in lung cancer, and it is an independent poor prognostic marker.[8] Two studies demonstrated PDGFR-α expression in lung cancer, and PDGFR-β was detected in stromal tissue only.[9,10] Another study also confirmed worse prognosis associated with PDGF and PDGFR expression.[11]

The presence of activated PDGFR-α is predictive of response to PDGFR inhibitor.[12]

Inhibition of PDGFRs in stromal cells leads to decreased interstitial fluid pressure and increased capillary-to-interstitium transport of small molecule, which could potentially result in the delivery of more chemotherapy to the tumor site.[13] This hypothesis is currently being tested through a phase II clinical trial of paclitaxel with Im in patients with NSCLC older than 70 years, clinical trial identification number NCT00408460. Thus, targeting the PDGF pathway is a reasonable approach and an attractive strategy given that PDGF inhibitors are readily available for evaluation.

Imatinib (Im) mesylate is primarily known as a protein-tyrosine kinase inhibitor of Bcr-Abl used in the treatment of chronic myelogenous leukemia. Im is also an inhibitor of stem cell factor CD117 receptor, known as C-KIT. Im inhibits PDGF and stem cell factor-mediated cellular events of cellular proliferation, gene expression, and cell migration. In preclinical studies, it enhanced the effect of chemotherapy agents such as 5 fluorouracil, paclitaxel, and cisplatin in lung cancer cells.[14,15] Uehara et al.[16] demonstrated that the Im and taxane combination had superior efficacy compared with either agent administered individually in a prostate cancer bone metastasis model. A phase I trial established the dose of D at 30 mg/m^2 weekly in combination with Im at 600 mg daily. They observed clinical activity with PSA decline in 14 patients (67%). These results suggest potential synergistic interaction between D and inhibition of PDGFR using Im.[17]

On the basis of these observations, we initiated a phase II study to assess the potential role of PDGFR inhibition, using Im in combination with D (ImD), in patients with recurrent NSCLC. Our primary objective was to determine the response rate of the combination. Secondary objectives included determination of the expression of PDGF-R, phosphorylated PDGF-R, and C-KIT in the available lung cancer tissue. We also analyzed the toxicity profile, time to progression (TTP), and overall survival of patients treated with this combination.

PATIENTS AND METHODS

The study was registered under clinical trials ID: NCT00222144. Adult patients with a histologic or cytologic diagnosis of NSCLC, documented recurrent or progressive disease by radiographic and/or clinical examination, and an Eastern Cooperative Oncology Group PS 0 to 1 were eligible. Subjects could have a maximum of two prior chemotherapy regimens excluding D, received prior EGFR therapy, or have clinically stable brain metastatic disease. Bidimensional measurable disease, adequate hematological, renal and hepatic function, and a forced expiratory volume-1 more than 800 ml were required. The forced expiratory volume-1 was an entry criterion to eliminate possible poor prognosis associated with patients with severe chronic obstructive pulmonary disease. Tumor samples for immunohistochemistry (IHC) analysis for PDGFR-α and β, their phosphorylated form, and C-KIT were requested but not mandated. The protocol was approved by Institutional Review Boards at the University of Kansas Medical Center and the Kansas City VA Medical Center. All patients were consented and informed of the investigational nature of the trial before initiation of the study procedures.

Study Treatment

D was given at 30 mg/m^2 IV weekly for 3 weeks and 1 week off. Patients received premedication with dexamethasone 4 mg orally for three doses beginning on the evening before D. Im was orally administered at 600 mg daily starting on day 1 of D treatment and continued while the patient was receiving D.

Patients had tumor assessment by radiographic examination every two cycles. After four cycles of ImD, patients with response or stable disease continued Im alone as maintenance until disease progression or for a total of 12 months. This study used the National Cancer Institute common toxicity criteria version 3.0 for toxicity and adverse event reporting. D was dose reduced if there were grade 3 or 4 hematologic toxicity. Im was dose reduced if there was grade 3 or 4 toxicity. Im also reduced if there was recurrence of grade 2 toxicity. Use of diuretics was allowed to treat edema related to D or Im.

Study Evaluation and Follow-Up

Prestudy evaluation included a complete medical history and physical examination including PS, laboratory analysis, pulmonary function tests, electrocardiogram, and baseline computed tomography scans of the measurable disease site, including chest and abdomen, 28 days before study entry. Response assessment occurred after every two cycles of ImD. Patients had complete blood count, chemistries, history, physical, and toxicity evaluation at the beginning of each cycle of ImD. Patients on the Im maintenance phase had a history and physical examinations, blood work, tumor assessment by radiographic examination, and toxicity evaluation every 2 months for total of 12 months or until disease progression. Patients could be removed from the study if unable to tolerate therapy due unacceptable toxicity, disease progression, development of an intercurrent, non–cancer-related illness that prevented study continuation, or patient refusal.

Immunohistochemical Studies

IHC stains for PDGFR-α, PDGFR-β, their respective phosphorylated form and C-KIT were performed on 4-μm thick sections cut from archived formalin-fixed paraffin embedded tissue blocks, when available. Commercially available antibodies against these markers were used per manufacturer's protocols, and staining was performed on a Dako Autostainer (Dako, Carpinteria, CA). Epitope retrieval using microwave heat or steam pretreatment was performed as required. Appropriate positive and negative tissue controls were performed with each run. All slides were evaluated by one pathologist who had no knowledge of the patient's clinical status. Cellular staining intensity was graded for each marker on a score from 0 to 3+. Staining characteristics was documented according to standard criteria, using a scale of 0 to 1+, 2+, 3+, according to the intensity of staining.

TABLE 1. Patient Characteristics

Patient Characteristics	$N = 23$
Age	Median 70 (54–83)
Female:male	2:21
PS, 0:1	2:21
Adenocarcinoma:squamous:nonspecified	6:3:14
White:African American	19:4
Prior therapy	
Surgery	6
Radiation therapy	17
First-line therapy—chemotherapy:erlotinib	22:1
Second-line therapy—chemotherapy:erlotinib	2:2
Third-line therapy with erlotinib	1

Eighteen had ImD as second-line therapy, four as third line, and one as fourth line.
ImD, Im in combination with D; PS, performance status.

Statistical Analysis

The primary objective was to evaluate the response rate of ImD in patients with recurrent NSCLC. Patients had to complete two cycles to be evaluable for response based on RECIST criteria. The secondary objectives were to determine the toxicity, PFS, overall survival, and expression of PDGF-R, phosphorylated PDGF-R, and C-KIT in the original tissue and correlate with response.

The treatment would be of interest if the proportion of patients with a favorable response was at least 35%, and it would be of no interest if the overall response was ≤15%. Thirty-two patients would be needed to test the null hypothesis: $p \leq 0.15$ and against the alternative hypothesis: $p \geq 0.35$ with 10% significance and 90% power. The rationale for this is given by Rogatko and Litwin.[18] The type I and II errors are 10%. We used a two-stage design under constraints to minimize the maximum sample size. The early stopping point was 20 patients. If three or fewer patients with a response were observed with 20 patients accrued, then the null hypothesis would be accepted, and the trial would be terminated. The probability of early stopping under the null hypothesis was 0.648 and under the alternative was 0.044. If the trial progressed until 32 patients were evaluated, it would require eight or more responding patients to reject the null hypothesis. Patients who did not receive two full cycles and not evaluable for response were replaced.

RESULTS

The study enrolled a total of 23 patients from January 2005 to December 2007. Patient characteristics are summarized in Table 1. The median age was 70 years with a range of 54 to 83 years. The majority of patients were men, white with PS of 1. The predominant histologic classification was non-small cell carcinoma, not otherwise specified. Twenty-two patients received a front-line platinum-based doublet, and one patient received erlotinib. Four patients had second-line therapy, and one patient had third-line therapy with erlotinib. Two patients had brain metastasis.

Twenty-three patients were enrolled, and 18 were evaluable for response. Five were not evaluable because they did not complete the required two cycles of therapy. One patient achieved a partial response (5.5%), four patients had stable disease, and 13 patients had progressive disease (72.2%). The disease control rate (partial response + stable disease) was 27.7%. The median TTP was 1.9 months (Figure 1), and the median overall survival was 6.1 months (Figure 2). Two patients who completed four cycles of therapy went on to maintenance therapy and had prolonged disease control with TTP of 7.78 months and 15.8 months. The study was stopped at 18 evaluable patients because two additional patients would not have altered study termination per the design criteria.

Toxicity

All 23 patients were evaluable for toxicity. A total of 39 cycles of ImD were administered. There was no grade 3 or 4 hematological toxicity. Adverse events possibly related to study treatment are described in Table 2 and included grade 3 dyspnea (two); grade 3 chest pain (one); grade 4 non-ST myocardial infarction (one); grade 3 hypokalemia (one);

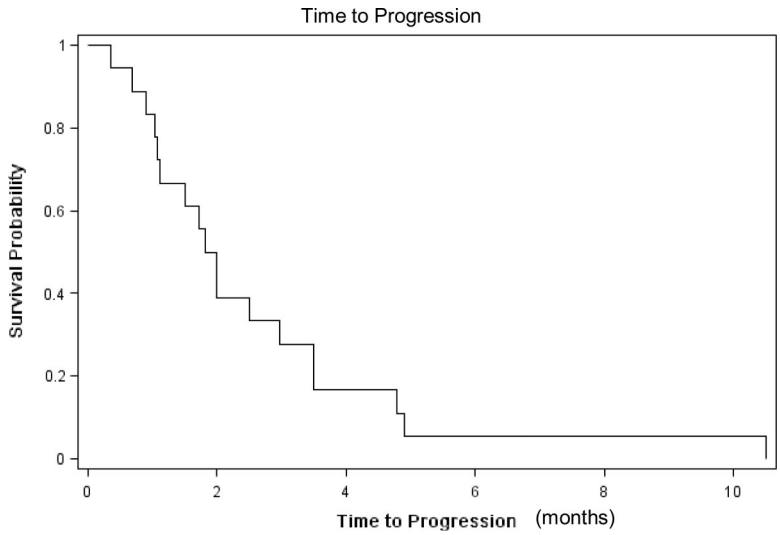

FIGURE 1. Time to progression.

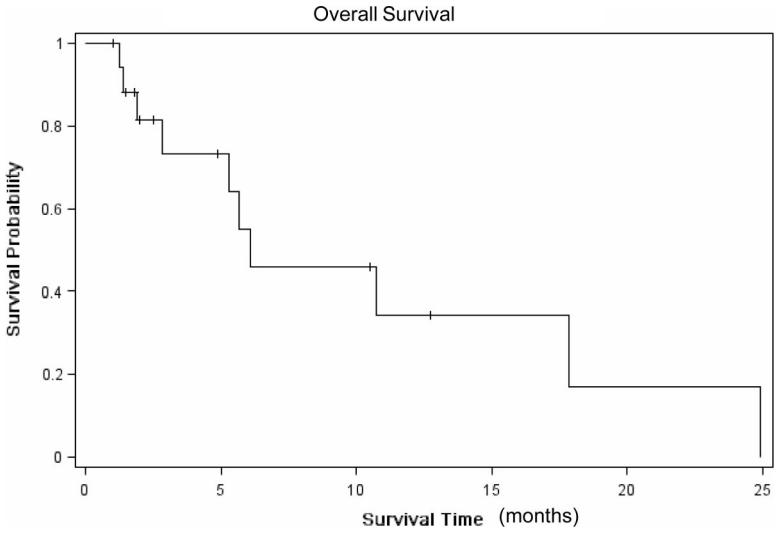

FIGURE 2. Overall survival.

TABLE 2. Grade 3/4 Adverse Event Possibly Related to Study Treatment

Adverse Events	*N*	Grade
Dyspnea	2	3
Chest pain	1	3
Non-ST MI with elevated troponin	1	4
Hypokalemia	1	3
Syncope	2	3

One death possibly due to study treatment.

TABLE 3. Immunohistochemistry Results, $N = 15$

	PGDFR α	pPDGFR α	PDGFR β	pPDGFR β	C-KIT
0–1+	11[a]	8	14	15	13
2+	2	1[b]	1	—	1
3+	2	6[b]	—	—	1

[a] Partial response.
[b] Stable disease.
PGDFR, platelet-derived growth factor receptor; pPGDFR, phosphorylated platelet-derived growth factor receptor.

grade 3 neurologic syncope (two). One possible treatment-related death occurred. We did observe seven patients who required Im dose reduction from 600 to 400 mg/d (three due to diarrhea, two due to cough, one due to increase liver function tests, and one due to nausea and vomiting).

The majority of patients ($n = 16$) discontinued the study due to disease progression, and seven patients discontinued treatment due to other reasons (one withdrew consent, one due to noncompliance, one due to loss to follow-up, one due to patient decision, one due to myocardial infarction before initiation of therapy, one due to MI during treatment, and death in one).

Immunohistochemical Results

We obtained tumor specimens from 15 patients and performed IHC analysis. The results are described in Table 3. More than 50% of the cases had staining in 75 to 100% of tumor cells (nine cases), and in the rest of the cases, there was at least expression in 50% in tumor cells (five cases) with only one case showing expression in 30% of tumor cells and one with no staining. We did not detect significant expression in the stroma. The majority of tumors had low biomarker expression (1+) across all the markers tested. Significant expression of 2 to 3+ was seen in four tumors (two adenocarcinoma and one squamous cell, and one not specified) (27%) for PDGF-α expression, and seven tumors (four adenocarcinoma, two squamous, and one not specified) (47%) had phosphorylated PDGFR-α. There was one case with 3+ C-KIT expression. The 2 to 3+ IHC results of the four patients with stable disease were as follows: one patient had 2+ phosphorylated PDGFR-α; one patient had 3+ phosphorylated PDGFR-α; and two patients did not have specimen available. The patient with the partial response had 1+ PDGFR-α in 100% of cells. A representative picture of tumor sample is in Figure 3.

DISCUSSION

In this small pilot study, the addition of Im to a weekly schedule of D did not meet the primary objective of an improvement in response rate in patients with relapsed NSCLC. A similar study conducted by White et al. also did not show significant activity in patients with recurrent NSCLC, with only one objective response in 10 patients. That study used the same dose of Im and D although it allowed prior D treatment. Three patients achieved stable disease, but all were of short duration.[19] Another phase II study from MD Anderson, clinical trials identification NCT01083589, using Im with D 60 mg/m^2 every 3 weeks in previously treated NSCLC, is currently ongoing. Studies with ImD have produced mixed results in other tumor types. ImD combination in platinum-resistant epithelial ovarian cancer showed a response rate of 21.7%. IHC expression of PDGFR, C-KIT, and PDGFR- β in tumor specimen did not predict response or PFS.[20] In metastatic breast cancer, ImD produced a response rate of 12%, median PFS of 3 months, and overall survival of 10 months in 18 evaluable patients.[21] In the

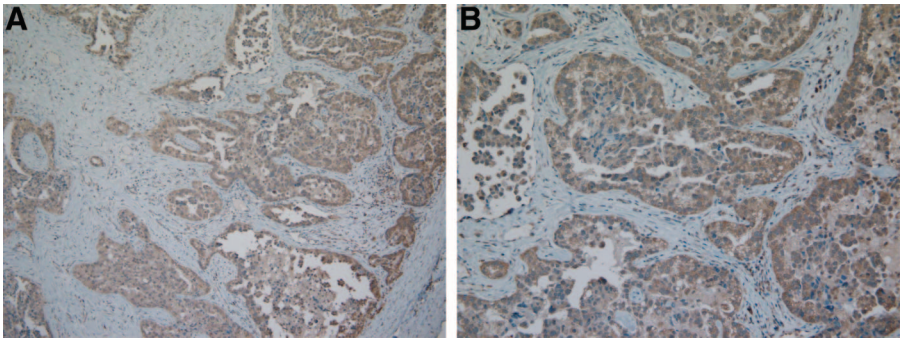

FIGURE 3. Representative example of immunostains for nonphosphorylated platelet-derived growth factor receptor (PDGFR)α in non-small cell lung adenocarcinoma. *A* and *B*, Two different magnifications of the tumor with moderate staining in the cytoplasm of tumor cells and minimal or absent staining in the surrounding stroma (immunostains: magnifications, $\times$100 [*A*] and $\times$400 [*B*]).

neoadjuvant setting of breast cancer, ImD yielded a response rate of 25%.[22]

There are several possible explanations for our negative outcome. We postulated that the mechanism of action of Im was predominantly angiogenesis inhibition through PDGF pathway blockade. In preclinical models, Im was a modestly potent inhibitor of PDGFR, but more potent inhibitors are available. Moreover, PDGF may not be a dominant angiogenesis promoter in relapsed NSCLC and requires coinhibition with other factors such as VEGF. Laboratory studies showed close interaction between the VEGF and PDGF systems with coactivation of the PDGF system when VEGF receptor is inhibited.[23,24] These studies support a combination strategy of VEGF and PDGFR-β inhibition with multiangiokinase inhibitors or dual agents. Angiokinases with multiple pathway inhibition, such as sorafenib, are currently in clinical trials. A phase II trial of sorafenib in relapsed NSCLC did not induce responses but produced stable disease in 59% of patients.[25] The University of Washington is conducting a pilot trial of bevacizumab and Im maintenance after a platinum doublet plus bevacizumab, clinical trials ID NCT00425646. This is an attractive strategy given our observation of prolonged disease stabilization (7.8 and 15.8 months) in two patients who went on to receive Im maintenance. Another possibility is to add a PDGFR inhibitor at the time of recurrence after bevacizumab maintenance or in first-line setting in conjunction with a VEGF receptor inhibitor.

D was given on a weekly basis as a means to enhance antiangiogenesis. D, similar to many chemotherapy agents, is known to possess antiangiogenic properties that are maximized when the drug is given on a more continuous basis.[26] Although there is controversy surrounding the efficacy of weekly D as being inferior to the every 3-week regimen, a meta-analysis comparing these two schedules did not show a difference in response rate or TTP or overall survival.[27] Therefore, it is unlikely that the schedule of D administration was responsible for the lack of antitumor activity seen in this study. A drug-drug interaction between Im and D is another possible explanation for the low response rate observed. D is a substrate for the CYP3A3/4 system. Im is also known to interact with the same isoenzyme and, therefore, could potentially lead to increased metabolism of D. Unfortunately, we did not design the study to look for pharmacological interaction between these two drugs.

The IHC data in a limited patient sample demonstrated that there is expression of PDGFR-α but no significant expression of PDGFR-β or C-KIT. This may explain the lack of significant activity of Im in our study, although two patients with stable disease had expression of PDGFRα and its phosphorylated form and both had prolonged TTP of 7.8 and 15.8 months. In retrospect, our selection of response rate and the magnitude of the benefit required to pursue this combination was overly ambitious. Perhaps, future studies using Im should be done in preselected patients with specific clinical characteristics (i.e., PS 0–1, absence of brain metastatic disease, and limited to second-line therapy) and positive expression of PDGFR or its phosphorylated form, looking at improvement of TTP at 6 months or 1-year overall survival as primary objective. The presence of C-KIT mutation predicts the activity of Im in gastrointestinal stromal tumors. Future studies in NSCLC should also perform analysis of C-KIT mutation.

The study regimen was well tolerated. We did not observe severe hematologic toxicities. The grade 3 nonhematological events were rare and atypical. Although classified as possibly related to study treatment, the events are commonly seen in this patient population.

CONCLUSIONS

PDGFR inhibition using ImD did not achieve the primary end point of improvement in response rate. This could be due to insufficient inhibition of angiogenesis through the PDGFR system by Im or combination of ImD; possible negative pharmacological interaction between D and Im with reduction in drug level; and low levels of expression of PDGFR in the patient population studied. A better understanding of the PDGFR pathway in lung cancer is needed to provide more rational therapeutic approaches. Inhibition of PDGFR using Im is potentially a new strategy in the treatment of cancer and deserves further investigation by combining it with another antiangiogenesis drug such as bevacizumab or other multitarget angiogenesis kinases, preferably in a group of patients with positive PDGFR expression and specific clinical characteristics. Correlation with C-KIT mutation should also be investigated. We would also suggest using PFS at 6 months as a primary end point in future clinical studies using these agents in recurrent NSCLC.

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