

Imatinib Mesylate in Combination With Docetaxel for the Treatment of Patients With Advanced, Platinum-resistant Ovarian Cancer and Primary Peritoneal Carcinomatosis

A Hoosier Oncology Group Trial

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BACKGROUND. Ovarian tumors frequently express c-Kit and/or platelet-derived growth factor receptors (PDGFRs). Imatinib mesylate blocks the growth of ovarian cancer cells in vitro and may enhance the activity of chemotherapy. This study was conducted to determine the activity of imatinib in combination with docetaxel in patients with recurrent, platinum-resistant epithelial ovarian cancer (EOC).

METHODS. Eligible patients had recurrent, platinum-resistant, or refractory EOC that expressed PDGFR α or c-kit, as determined by immunohistochemistry. Imatinib mesylate at a dose of 600 mg orally once daily was administered continuously with docetaxel at a dose of 30 mg/m² given intravenously once weekly in Weeks 1 through 4 of every 6-week cycle. The primary endpoint was objective response rate (ORR) as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST).

RESULTS. Thirty-four patients were screened for PDGFR α and c-kit expression to enroll 23 patients between December 2003 and October 2005. Four patients had c-kit-positive/PDGFR-negative tumors, 11 patients had PDGFR-positive/c-kit-negative tumors, and 8 patients had c-kit-positive/PDGFR-positive tumors. The median patient age was 56 years (range, 33-76 years). Patients had received a median of 3 prior treatments. The ORR was 21.7% and included 1 complete and 4 partial responses. An additional 3 patients had stable disease for more than 4 months. Expression of PDGFR, c-kit, phosphatase and tensin homolog (PTEN), and phosphorylated protein kinase B (Akt) did not predict response to therapy. The most common adverse events encountered were fatigue (83%), nausea (74%), diarrhea (61%), anorexia (52%), and edema (65%), and the majority of those events were graded as grade 1 or 2.

CONCLUSIONS. The combination imatinib and docetaxel was tolerated in patients with heavily pretreated EOC that expressed c-kit or PDGFR α . Few patients had sustained responses or stable disease. *Cancer* 2008;113:723-32. © 2008 American Cancer Society.

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Epithelial ovarian cancer (EOC) is the leading cause of mortality among gynecologic malignancies.¹ Treatment relies on surgical debulking and platinum-based chemotherapy. Unfortunately, most patients develop disease recurrence and become resistant to platinum-based therapy. Subsequent chemotherapy offers only limited and temporary benefit.^{2,3} The need for more effective therapies that are rooted firmly in an understanding of the biologic mechanisms that drive tumor growth is both real and pressing.⁴ Clinical trials to test inhibitors of growth factor receptors important to EOC progression are ongoing.

The platelet-derived growth factor receptors (PDGFR) α and β are transmembrane receptor tyrosine kinases activated by PDGF.^{5,6} They are implicated in a variety of physiologic and pathologic processes, including cell growth and survival,⁷ transformation,⁸ migration, vascular permeability, stroma modulation, and wound healing.⁹ Ligand-induced receptor activation promotes receptor dimerization and interaction with phosphoinositide 3-kinase (PI3K), phospholipase γ C, guanosine triphosphatase-activating protein, and Src kinases¹⁰; and intracellular signaling promotes cell proliferation and survival. Aside from these effects, the PDGFR is important functionally to the modulation of stroma, regulating its interstitial pressure, permeability, and neovascularization.¹¹⁻¹³ Consequently, PDGFR blockade affects tumor cells directly and also affects the tumor microenvironment, increasing stroma permeability, inhibiting angiogenesis, and enhancing the delivery of chemotherapy.^{14,15}

We initially identified PDGFR over expression in EOC cells by using microarray hybridization and comparative analysis between primary cells derived from ovarian tumors and primary cells derived from the normal ovarian epithelium.¹⁶ The findings were confirmed by others,¹⁷⁻¹⁹ and PDGFR expression was linked to poor clinical outcome¹⁷ and aggressive tumor characteristics.^{20,21} To date, no activating PDGFR or c-kit mutations have been identified in EOC.²² However, we observed that the PDGFRs and their ligands, PDGFA, PDGFB, PDGFC, and PDGFD, are coexpressed in ovarian tumors and that PDGF is secreted in ascites fluid.²³ These observations indicate that the receptor may be activated through autocrine or paracrine mechanisms in the peritoneal milieu.

Imatinib mesylate (Gleevec; Novartis) is a 2-phenylaminopyrimidine derivative that selectively inhibits the abl, c-kit, and PDGFR tyrosine kinases.²⁴ Imatinib has been studied extensively in chronic myelogenous leukemia²⁵ and in malignancies governed by abnormally activated PDGFR or c-kit receptors.²⁶ We observed that imatinib inhibited the proliferation of ovarian cancer cells in vitro¹⁹ and decreased vascular endothelial growth factor secretion by EOC cells,²⁷ findings that supported its clinical investigation in ovarian cancer. However, imatinib had little activity as monotherapy in 4 previous phase 2 studies in ovarian cancer²⁸⁻³⁰ (including 1 Gynecologic Oncology Group study with unpublished results).

Because PDGFRs are highly expressed and functional in fibroblasts, pericytes, and endothelial cells, we hypothesized that PDGFR inhibition affects the tumor microenvironment, modulating the interstitial pressure and angiogenesis,²⁷ and enhancing delivery of chemotherapy, as suggested previously in preclinical models.^{13,15,31,32} We set out to test this hypothesis in a clinical trial combining chemotherapy with imatinib. Synergy between imatinib and docetaxel had been observed in other tumor models.^{32,33} In addition, our unpublished preclinical data indicated that the addition of imatinib lowers 10-fold the 50% inhibitory concentration for docetaxel in EOC cells that over express protein kinase B (Akt), suggesting that this combination may overcome Akt-induced chemoresistance. It has been established that activation of the survival PI3K/Akt pathway is common in EOC and has been implicated in resistance to chemotherapy.^{34,35} Therefore, we studied imatinib in combination with weekly docetaxel in patients with recurrent, platinum-resistant, or refractory EOC who had tumors that expressed PDGFR α or c-kit using a dose and schedule that was defined in a previous phase 1 study.³⁶ The primary objectives of this study were to determine the overall response rate and the tolerability of the regimen.

MATERIALS AND METHODS

Patient Population

Patients with advanced, histologically documented EOC that recurred within 6 months after platinum-based chemotherapy were eligible for screening. Consenting patients were screened for PDGFR α or c-kit expression using immunohistochemistry (IHC).

Staining of archival tumor was performed in the Department of Pathology at Indiana University. Only patients who harbored PDGFR α - or c-kit-positive tumors (at least 1+ by IHC) were eligible for treatment. Patients with both measurable and detectable disease were eligible. Measurable disease was defined according to Response Evaluation Criteria in Solid Tumors (RECIST).³⁷ Patients with nonmeasurable disease could enroll if they had clinically or radiologically detectable disease (eg, ascites, mesenteric thickening) and 2 consecutive rising pretreatment serum CA 125 levels >2-fold the nadir or 1 CA 125 measurement >100 IU/mL.

All patients were aged ≥ 18 years, had an Eastern Cooperative Oncology Group performance status (PS) between 0 and 2, and had a life expectancy of at least 12 weeks. Other eligibility criteria included no upper limit to the number of prior therapies allowed and adequate hematologic, hepatic, and renal function. Key exclusion criteria included prior treatment with any experimental anticancer agent within 4 weeks of Day 1, prior treatment with docetaxel or imatinib, a history of brain metastases, clinical evidence of small bowel obstruction or refractory ascites, and use of oral anticoagulation. Prior exposure to paclitaxel was allowed. All patients provided written informed consent, and the protocol was approved by institutional review boards.

Treatment Plan

Treatment consisted of docetaxel at a dose of 30 mg/m² intravenously weekly for 4 of 6 weeks and imatinib at a dose of 600 mg orally once daily administered continuously. Each cycle was 6 weeks, and treatment was continued for a maximum of 6 cycles (36 weeks) or until disease progression or intolerable toxicity. The dose selected was based on a phase 1 study performed in patients with prostate cancer.³⁶ Patients discontinued therapy if they had recurrent grade 3 or 4 toxicity, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE), version 3.0; any subjectively intolerable toxicity; or progressive disease. Dexamethasone was given orally every 12 hours for 3 doses with each docetaxel infusion.

Efficacy and Toxicity Assessment

Tumor burden was evaluated at baseline by clinical and image-based evaluation, including computed tomography scans of the abdomen and pelvis. The investigator-determined best overall response was defined using RECIST for measurable tumors and Gynecological Cancer Intergroup CA-125 response criteria for nonmeasurable tumors.³⁸ CA 125 meas-

urements were obtained from all patients on Day 1 of each cycle. Objective response by radiographic criteria was assessed before Cycle 3 and Cycle 5 and at the end of treatment. Adverse events were assessed on Day 1 of each cycle and were graded according to NCI-CTCAE (version 3).

IHC

Paraffin-embedded tumor specimens from the time of diagnostic surgery were collected at enrollment from consenting patients and immunostained for PDGFR α and c-kit. The antibody for PDGFR α was obtained from R&D Systems (Minneapolis, Minn) at a concentration of 20 μ g/mL, and the antibody to c-kit was obtained from Oncogene (25 μ g/mL; Upstate, Waltham, Mass). Secondary labeling was based on the avidin/biotin system (LSAB2 kit; Dako). Slides were stained with 3-3' diaminobenzidine and counterstained with hematoxylin. Negative controls with omission of the primary antibody and positive controls for PDGFR α and c-kit were run in parallel. Staining was graded from 0 (no staining) to 3+ (strong staining) by a board-certified pathologist (R.E.E.), and the percentage of stained cells was noted. Immunoreactivity was recorded only if it was observed in >15% to 20% of tumor cells. Patients were deemed eligible for treatment if either PDGFR α or c-kit staining was graded at least 1+ in 20% of tumor cells. After enrollment, archival tumors also were stained for PDGFR β primary antibody (Santa Cruz Biotechnology, Inc.; dilution, 1:200), phosphorylated PDGFR α primary antibody (Santa Cruz Biotechnology, Inc.; dilution, 1:50), serine 473 (Ser⁴⁷³) phosphorylated Akt primary antibody (Cell Signaling; dilution, 1:1000), and PTEN primary antibody (Cell Signaling Technology; dilution, 1:50). Positive and negative controls were run in parallel, and staining was graded from 0 (no staining) to 3+ (strong staining). The pathologist (R.E.E.) was blinded to the specimens' identity and corresponding clinical information.

Statistical Analysis

This was an open-label, multicenter study performed through the Hoosier Oncology Group (protocol Gyn 03-62). The primary objective was measurement of the overall response rate (ORR), including complete responses (CR) and partial responses (PR). The secondary objectives were assessment of toxicity, measurement of progression-free survival (PFS) and overall survival (OS), and assessment of molecular predictors of response. In particular, Akt activation was evaluated as a biomarker of resistance to therapy. PFS was defined as the time from Day 1 of treatment to the time of documented disease progression

TABLE 1
Characteristics of Immunostaining for Platelet-derived Growth Factor Receptor- α and c-kit in Registered Patients

Patient Group	No. of Patients		Total
	PDGFR+	PDGFR-	
Patients screened			
C-kit+	11	5	16
C-kit-	14	4	18
Total	25	9	34
Patients enrolled			
C-kit+	8	4	12
C-kit-	11	0	11
Total	19	4	23

PDGFR indicates platelet-derived growth factor receptor; +, positive; -, negative; C-kit; cell-surface glycoprotein (CD117).

or death. OS was defined as the time from Day 1 of study to the time of death. Duration of response was defined as the time from the initial CR or PR to the time of disease progression or death. The tested null hypothesis of no efficacy is that the response rate of the experimental treatment is no higher than 20%. With 23 patients, if the true response rate of the experimental treatment would be $\geq 40\%$, then a 1-sided exact test for a single proportion has 76% power at the 10% α level to reject the null hypothesis, and we would conclude that this combination is clinically interesting.

Demographic and baseline characteristics were summarized by using medians (with ranges) for continuous variables and proportions for categorical variables. Median PFS and OS were estimated by using the Kaplan-Meier method. Correlations between clinical response and level of IHC staining for different molecular biomarkers were assessed with the Fisher exact test.

RESULTS

Patients

Thirty-four consenting patients with recurrent EOC underwent prospective screening by IHC for PDGFR α and c-kit expression in archival tissue. Sixteen specimens were immunoreactive for c-kit, including 11 specimens that also were positive for PDGFR α . In total, 25 patients had PDGFR α -expressing tumors. Of all screened patients, 23 were enrolled and treated: Twelve patients had c-kit-positive tumors, 19 patients had PDGFR α -positive tumors, and 8 patients had tumors that expressed both PDGFR α and c-kit (Table 1) (Fig. 1).

Patient characteristics are presented in Table 2 and indicate that 22 patients developed recurrent

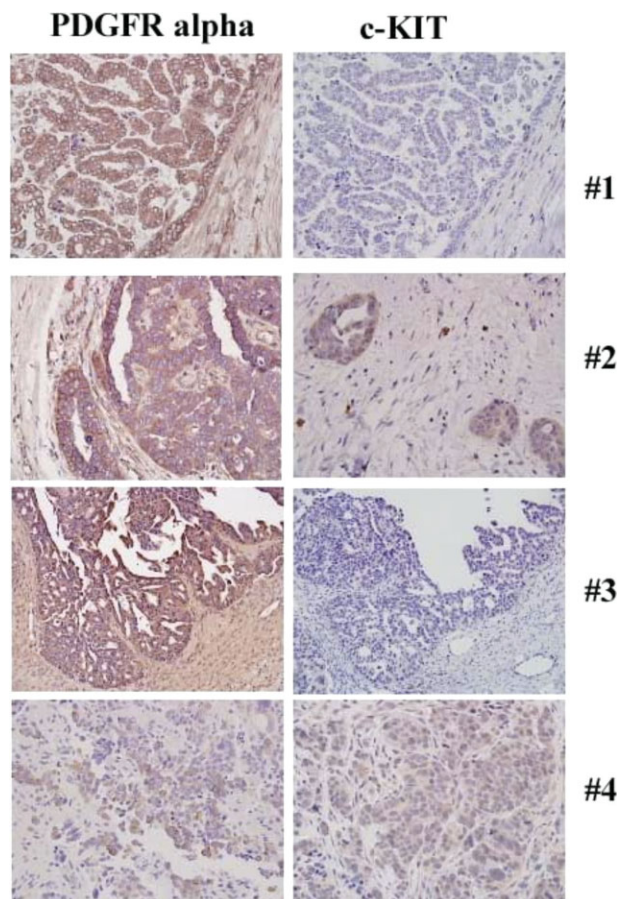


FIGURE 1. Immunohistochemical staining for platelet-derived growth factor receptor α (PDGFR α) and c-kit obtained at screening. Representative tumor sections photographed at $\times 100$ magnification are shown. Specimens 1 and 3 were positive for PDGFR α and negative for c-kit, Specimen 2 displayed strong positive staining for both receptors, and Specimen 4 was weakly positive for PDGFR α and for c-kit.

disease during or within 6 months of receiving a prior platinum-containing regimen. Of those, 7 patients had platinum-refractory disease (progression through a platinum-based chemotherapy regimen), and 15 patients had platinum-resistant disease (progression within 6 months after completing platinum-based chemotherapy). One patient was allergic to platinum. Nineteen patients had measurable disease. The median number of prior chemotherapy regimens was 3 (range, 1-9 prior chemotherapy regimens), and the median patient age was 56 years (range, 33-76 years). The majority of patients had high-grade tumors that originated the ovary with a serous papillary histologic pattern.

Treatment Administration and Safety

Fifty-six cycles of chemotherapy were administered, and patients were on treatment for a median of 12

TABLE 2
Patient Characteristics

Characteristic	No. of Patients
Patients enrolled	23
Age, y	
Median	56
Range	33-76
ECOG PS	
0	19
1	4
Race, white	23
Primary tumor site	
Ovary	18
Fallopian tube	1
Primary peritoneal	2
Not known	2
Histologic subtype	
Serous papillary	19
Clear cell	1
Endometrioid	1
Not known	2
Histologic grade	
1	0
2	6
3	15
Not known	2
No. of prior therapies	
Median	3
Range	1-9
No. of patients with ≥3 prior Tx	16
No. of patients ≥4 prior Tx	11
Platinum-sensitivity	
Refractory	7
Resistant	15
Allergic	1
Measurable disease (RECIST)	21
Detectable disease	2

ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; Tx, treatment; RECIST, Response Evaluation Criteria in Solid Tumors.

weeks (2 cycles; range, 1-6 cycles). Causes for treatment discontinuation were disease progression (14 patients), toxicity (5 patients), completion of therapy (2 patients), and withdrawal of consent (2 patients). Table 3 lists adverse events that occurred during the study irrespective of relatedness. The most common adverse events encountered were fatigue (83%), nausea (74%), diarrhea (61%), anorexia (52%), and edema (65%). The majority of these episodes were categorized as grade 1 or 2. There were 4 grade 4 events, including 2 episode of leukopenia, 1 episode of neutropenia, and 1 episode of fatigue, all of which were considered related to treatment. There was 1 episode of grade 3 thrombocytopenia and 3 episodes of fever, including 1 that was associated with grade 4 neutropenia. Other specific toxicities included rash observed in 7 patients (2 episodes were grade 3), ve-

TABLE 3
Toxicity*

Toxicity, CTCAE v3	No. of Patients (%)		
	Grade 3	Grade 4	All Grades
Leukopenia	—	2 (8.7)	
Neutropenia	—	1 (4.3)	
Anemia	—	—	8 (35)
Thrombocytopenia	1 (4.3)	—	4 (17)
Fever			
ANC >500 cells/mm ³	2 (8.7)	—	7 (30)
ANC <500 cells/mm ³	1 (4.3)	—	1 (4.3)
Fatigue	5 (21.7)	1 (4.3)	19 (83)
Ascites (nonmalignant)	1 (4.3)	—	1 (4.3)
Pleural effusion (nonmalignant)	1 (4.3)	—	1 (4.3)
Edema	—	—	15 (65)
Rash	2 (8.7)	—	7 (30)
Thromboembolism	2 (8.7)	—	2 (8.7)
Anorexia	—	—	12 (52)
Diarrhea	1 (4.3)	—	14 (61)
Constipation	—	—	8 (35)
Nausea	3 (13)	—	17 (74)
Dysgeusia	—	—	9 (39)
Hypokalemia	4 (17)	—	6 (26)
Hypocalcemia	1 (4.3)	—	8 (35)
Mood alteration (depression, anxiety)	—	—	7 (30)

CTCAE v3 indicates Common Terminology Criteria for Adverse Events version 3.0; ANC, absolute neutrophil count.

*Adverse events encountered in at least 10% of patients irrespective of relatedness.

nous thromboembolism in 3 patients, hypokalemia in 6 patients (4 episodes were grade 3), and hypocalcemia in 8 patients (1 episode was grade 3). No deaths were recorded during treatment. Four serious adverse events were reported, all of which were considered treatment-related by the investigator: These included 2 episodes of febrile neutropenia, 1 episode of nausea and vomiting, and 1 episode of anemia and fatigue. Two of the patients who had such events discontinued therapy.

Efficacy

All enrolled patients were included in the analysis of efficacy. The ORR was 21.7%, including 1 CR and 4 PRs, all determined by RECIST. The PRs were confirmed by repeat scans, but the CR was not confirmed, because this patient had recurrent grade 3 rash and discontinued imatinib to pursue therapy with docetaxel alone after 2 cycles. The Kaplan-Meier estimate of median duration of response has not been achieved. One of the 5 responders developed disease recurrence 1.1 months after achieving a response. The other 4 responders were still in remission at the time of data completion. Three additional patients who did not reach a PR had stable disease

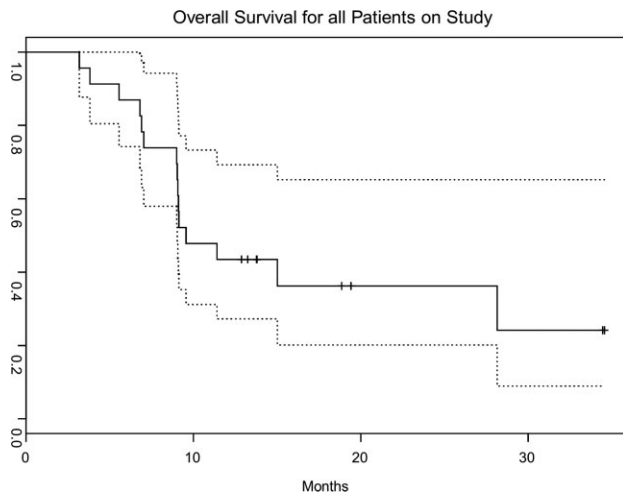


FIGURE 2. Kaplan-Meier estimate of overall survival.

that lasted between 4.2 months and 9 months. The median PFS was 1.77 months (95% confidence interval [95% CI], 1.38-3.78 months), the median OS was 9.56 months (95% CI, 9.03-28.16 months) (Fig. 2), and the median follow-up was 18.86 months (95% CI, 13.77-34.46 months). Among the patients deriving clinical benefit, which was defined either as stable disease or as an objective response, 3 patients had PDGFR α -positive tumors, 2 patients had c-kit-positive tumors, and 3 patients had tumors that expressed both PDGFR α and c-kit. IHC staining characteristics of the patients who derived clinical benefit are detailed in Table 4.

Molecular Predictors of Response

To identify molecular predictors of response, archival tumors were analyzed retrospectively for the expression of proteins implicated in PDGFR signaling. On the basis of our preclinical data¹⁹ and other reports implicating Akt in resistance to chemotherapy,^{19,35} we speculated that activation of Akt would predict resistance to treatment. Therefore, tumors were immunostained for Ser⁴⁷³ phosphorylated Akt (pAkt). We observed that the majority of ovarian tumors expressed activated Akt, with moderate (2+) or strong (3+) Akt staining noted in all but 2 tumors (Fig. 3) (Table 5), confirming previous reports that this pathway is highly activated in EOC.³⁴ It is interesting to note that we observed both nuclear and cytoplasmic pAkt staining: Eleven 11 tumors displayed moderate or strong cytoplasmic pAkt staining, and 19 tumors displayed 2+ to 3+ nuclear immunoreactivity. The significance of nuclear localization of Akt in ovarian cancer cells is not clear; emerging reports suggest that cellular sublocalization of Akt

TABLE 4
Platelet-derived Growth Factor Receptor α and C-kit Staining in Patients Deriving Clinical Benefit (Complete Response, Partial Response, or Stable Disease)

Response	No. of Patients		Total
	PDGFR+	PDGFR-	
PR			4
C-kit+	1	2	
C-kit-	1	0	
CR			1
C-kit+	0	0	
C-kit-	1	0	
SD			3
C-kit+	2	0	
C-kit-	1	0	
Total	6	2	8

PDGFR indicates platelet-derived growth factor receptor; +, positive; -, negative; PR, partial response; C-kit, cell-surface glycoprotein (CD117); CR, complete response; SD, stable disease.

has specific functional roles in other tumors.³⁹ However, we did not observe a correlation between pAkt (either nuclear or cytoplasmic) and clinical response or PFS (Fisher exact test; $P = .65$).

We also assessed the expression of the phosphatase PTEN, a critical regulator of Akt activity. PTEN expression (0 staining) was absent in ovarian tumor cells in 9 of 23 tumors; 11 ovarian tumors expressed PTEN weakly (1+). The PTEN level did not correlate with response or clinical benefit (Fisher exact test; $P = .33$).

Phosphorylation of PDGFR α also was measured by IHC, and moderate staining (2+) was recorded only in 4 samples. Intense immunoreactivity (3+) was not observed. Clinical response or PFS did not correlate with the presence of PDGFR α phosphorylation (Fisher exact test; $P = .27$).

Finally, we evaluated expression of the related receptor, PDGFR β . Because the β receptor is expressed strongly in stroma rather than in the epithelial component of tumors, and because no differential expression of the β receptor has been recorded between nontransformed and transformed EOC cells,¹⁸ we chose not to use PDGFR β as criterion for patient selection. However, we investigated its expression retrospectively and observed that 20 of 23 tumors strongly expressed PDGFR β (2+ to 3+ immunoreactivity). Its expression did not correlate with response or with PFS.

DISCUSSION

The PDGF and c-kit receptors are expressed in EOC, and their targeting is supported by preclinical

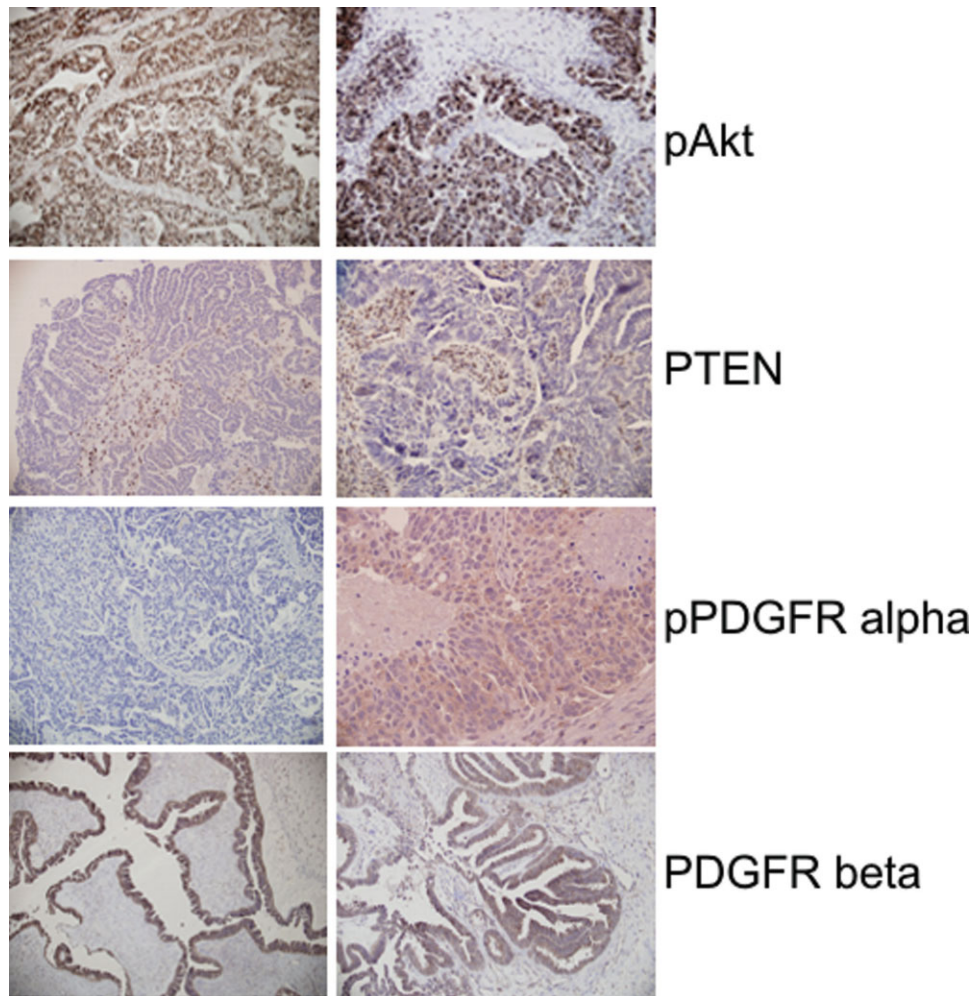


FIGURE 3. Immunohistochemical staining for serine 473 (Ser⁴⁷³), phosphorylated protein kinase B (pAkt), phosphatase and tensin homolog (PTEN), phosphorylated platelet-derived growth factor receptor α (pPDGFR α), and PDGFR β . Representative tumor sections photographed at $\times 100$ or $\times 200$ magnification are shown. Generally, there was intense staining for Ser⁴⁷³ pAkt. PTEN expression generally was low in tumor cells but was present in stroma and vascular structures. pPDGFR α staining generally was weak in tumor cells, whereas PDGFR β was expressed strongly in epithelial cells and stroma in most tumors.

models.²⁰ Aside from direct effects on tumor cells, PDGFR blocking agents modulate stroma by altering permeability and angiogenesis and facilitate the penetrance of chemotherapy in the tumor milieu.^{14,15} The goal of this phase 2 trial was to assess the safety and efficacy of imatinib in combination with docetaxel in patients with recurrent, platinum-resistant, or refractory ovarian cancer.

The regimen was tested and deemed feasible in a modular phase 1 trial; dose-limiting toxicities were fatigue, vomiting, diarrhea, and pulmonary edema.³⁶ In the current trial, the combination was tolerated well; however, regimen-specific toxicities were recorded. For instance, rash was observed in 7 patients (30%), and 2 of those episodes were assessed as grade 3. Typically, the rash occurred dur-

ing the first cycle and was responsive to interruption of therapy and supportive care. In most patients, imatinib was tolerated upon restarting treatment in incremental doses and did not lead to treatment discontinuation. The frequency of rash was higher than previously reported in men who were enrolled in the phase 1 trial³⁶ and higher than recorded with imatinib mesylate monotherapy.²⁹ Fatigue was a common effect of treatment, consistent with the known profile of docetaxel⁴⁰ and possibly compounded by the addition of imatinib. Despite the routine use of steroids, another common toxicity was edema and/or accumulation of peritoneal or pleural fluid, which was observed in 15 of 23 treated patients and may have reflected an untoward effect of PDGFR blockade. Previous use of an antibody directed against

TABLE 5
Expression of Other Molecular Markers in Rapport With Clinical Response

Clinical Response	No. of Patients			
	Cytoplasmic pAkt	PTEN	PDGFR β *	pPDGFR α *
PR or CR (n=5)				
Positive	3	4	5	3
Negative	2	1	0	2
SD (n=3)				
Positive	0	1	3	3
Negative	3	2	0	0
PD (n=15)				
Positive	8	6	12	13
Negative	6	7	2	2
N/A	1	2	1	0

pAkt indicates phosphorylated protein kinase B; PTEN, phosphatase and tensin homolog; pPDGFR, phosphorylated platelet-derived growth factor receptor; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease; N/A, tumor specimen not available for staining.

*For pAkt, pPDGFR α and PDGFR β , "positive staining" was defined as samples that displayed from 2 to 3+ immunoreactivity in at least 20% of tumor cells. For PTEN, any level of immunoreactivity (including 1+) was considered positive.

PDGFR β was associated with increased interstitial fluid pressure and edema,⁴¹ likely because of inhibition of PDGFR β -expressing stromal cells. The use of docetaxel in combination with imatinib may have accentuated this adverse event. In patients with ovarian cancer, in which fluid retention is a common symptom of the disease, this type of toxicity may be a confounding factor (ie, increased ascites), accentuating the common clinical manifestations of EOC. Further development of PDGFR inhibitors for ovarian cancer should take into account this anticipated effect.

To enrich the patient population for the presence of one of the targets of imatinib, we preselected patients on the basis of PDGFR α and c-kit expression by IHC. We observed that approximately 50% of the screened tumors (16 of 34 samples) expressed c-kit. However, most staining was weak (1+), and only 2 tumors displayed moderately intense immunoreactivity (2+). It is generally accepted that c-kit overexpression is not a common event in EOC, although there are reports noting a higher rate of expression than what we observed in the current study.^{18,42,43} In contrast, PDGFR α and PDGFR β are expressed widely,^{17,18,23} and this was confirmed by our findings, in which 25 of 34 tumors stained strongly for PDGFR α , and 20 of 23 tumors stained intensely for the β receptor.

In this prospectively selected group of patients, we observed 5 objective responses and 3 patients with prolonged disease stabilization (>4 months), for

a rate of clinical benefit of 35%. It is noteworthy that the responses tended to be sustained, and the median duration of response was not reached. At least 2 of the PRs occurred after a lag of at least 3 months of treatment, later than what typically would be expected with cytotoxic therapy, a pattern that suggests potential benefit from adding the biologic agent (eg, imatinib) to docetaxel. However, the observed ORR (21.7%) did not meet preset criteria for deeming the combination clinically interesting. On the basis of prior reports of clinical trials with docetaxel in EOC, we had estimated that the ORR to docetaxel monotherapy would be approximately 20%.^{40,44-46} However, the group of patients enrolled here was heavily pretreated, and approximately 50% had received ≥ 4 prior treatments. All but 1 patient had failed on platinum within 6 months, and all 23 patients had received and failed on taxanes. Therefore, in retrospect, the preset bar of 20% may have been too high for this group of patients. Another mitigating factor was the choice of weekly dosing for docetaxel. There is limited experience with weekly docetaxel in EOC^{47,48}; and, based on data from other malignancies, it is possible that weekly regimens may be less effective than the standard dose,⁴⁹ which would explain a lower ORR than anticipated. However, weekly paclitaxel has been studied in EOC, and responses have been documented in patients with demonstrated resistance to platinum/paclitaxel delivered on an every-3-week schedule.^{50,51} Thus, we cannot exclude the possibility that the observed effects in the current study may have been caused by the use of weekly taxane.

We did not identify molecular predictors of response among several proteins tested. Neither expression of PDGFR α , PDGFR β , or c-kit nor activation of PDGFR α (eg, phosphorylation) or Akt (eg, pAkt) were predictors. We recognize a limitation of the study is that we did not have access to fresh biopsies to assess the expression of markers in 'real time.' It is possible that tumor characteristics are altered as disease progresses and becomes resistant to chemotherapy. The molecular features at the time of diagnosis, assessed by using archival tissue, may differ significantly from what would be observed several lines of therapy later. However, obtaining fresh tumor tissue from patients with advanced cancer often is limited by clinical, ethical, and financial constraints.⁵² Other variability in biomarker data, and particularly in the assessment of phosphorylated (activated) proteins, may be related to technical aspects, such as procurement and preservation of tumor tissue without activating phosphatases. This may be a confounding factor, because the tissues

that we used in the current study were obtained from multiple institutions using different procedures for tissue fixation and preservation.

In conclusion, the current trial confirmed that the expression of PDGFR is common in EOC, more so than c-kit expression, and demonstrated the feasibility of a combined approach using chemotherapy and PDGFR inhibition. The combination of imatinib and docetaxel induced few responses in heavily pretreated patients with platinum-resistant ovarian cancer. However, there was no clear benefit of this combination over docetaxel alone. Because imatinib had limited activity as monotherapy in EOC, further exploration of PDGFR blockade should focus on the effects of imatinib or other PDGFR inhibitors on stroma, modulation of angiogenesis, and facilitation of chemotherapy delivery.

REFERENCES

- Greenlee RT, Murray T, Bolden S, et al. Cancer statistics, 2000. *CA Cancer J Clin.* 2000;50:7-33.
- Ozols R, Schwartz P, Eifel P. Ovarian cancer, fallopian tube carcinoma and peritoneal carcinoma. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* Philadelphia, Pa: Lippincott-Raven;1997:1502-1539.
- Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol.* 2001;19:3312-3322.
- Bookman MA, Darcy KM, Clarke-Pearson D, et al. Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: a phase II trial of the Gynecologic Oncology Group. *J Clin Oncol.* 2003;21:283-290.
- Hart CE, Forstrom JW, Kelly JD, et al. Two classes of PDGF receptor recognize different isoforms of PDGF. *Science.* 1988;240:1529-1531.
- Eriksson A, Siegbahn A, Westermarck B, et al. PDGF alpha and beta-receptors activate unique and common signal transduction pathways. *EMBO J.* 1992;11:543-550.
- Yao R, Cooper GM. Requirement for phosphatidylinositol-3 kinase in the prevention of apoptosis by nerve growth factor. *Science.* 1995;267:2003-2006.
- Huang JS, Huang SS, Deuel TF. Transforming protein of simian sarcoma virus stimulates autocrine growth of SSV-transformed cells through PDGF cell-surface receptors. *Cell.* 1984;39:79-87.
- Greenhalgh DG, Sprugel KH, Murray MJ, et al. PDGF and FGF stimulate wound healing in the genetically diabetic mouse. *Am J Pathol.* 1990;136:1235-1246.
- Heldin CH, Ostman A, Ronnstrand L. Signal transduction via platelet-derived growth factor receptors. *Biochim Biophys Acta.* 1998;1378:F79-F113.
- Yu J, Moon A, Kim HR. Both platelet-derived growth factor receptor (PDGFR)-alpha and PDGFR-beta promote murine fibroblast cell migration. *Biochem Biophys Res Commun.* 2001;282:697-700.
- Cao R, Brakenhielm E, Li X, et al. Angiogenesis stimulated by PDGF-CC, a novel member in the PDGF family, involves activation of PDGFR-alpha and -beta receptors. *FASEB J.* 2002;16:1575-1583.
- Bergers G, Song S, Meyer-Morse N, et al. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *J Clin Invest.* 2003;111:1287-1295.
- Pietras K, Rubin K, Sjoblom T, et al. Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy. *Cancer Res.* 2002;62:5476-5484.
- Baranowska-Kortylewicz J, Abe M, Pietras K, et al. Effect of platelet-derived growth factor receptor-beta inhibition with STI571 on radioimmunotherapy. *Cancer Res.* 2005;65:7824-7831.
- Matei D, Graeber TG, Baldwin RL, et al. Gene expression in epithelial ovarian carcinoma. *Oncogene.* 2002;21:6289-6298.
- Henriksen R, Funai K, Wilander E, et al. Expression and prognostic significance of platelet-derived growth factor and its receptors in epithelial ovarian neoplasms. *Cancer Res.* 1993;53:4550-4554.
- Schmandt RE, Broaddus R, Lu KH, et al. Expression of c-ABL, c-KIT, and platelet-derived growth factor receptor-beta in ovarian serous carcinoma and normal ovarian surface epithelium. *Cancer.* 2003;98:758-764.
- Matei D, Chang DD, Jeng MH. Imatinib mesylate (Gleevec) inhibits ovarian cancer cell growth through a mechanism dependent on platelet-derived growth factor receptor alpha and Akt inactivation. *Clin Cancer Res.* 2004;10:681-690.
- Lassus H, Sihto H, Leminen A, et al. Genetic alterations and protein expression of KIT and PDGFRA in serous ovarian carcinoma. *Br J Cancer.* 2004;91:2048-2055.
- Spentzos D, Levine DA, Ramoni MF, et al. Gene expression signature with independent prognostic significance in epithelial ovarian cancer. *J Clin Oncol.* 2004;22:4700-4710.
- Sihto H, Sarlomo-Rikala M, Tynninen O, et al. KIT and platelet-derived growth factor receptor alpha tyrosine kinase gene mutations and KIT amplifications in human solid tumors. *J Clin Oncol.* 2005;23:49-57.
- Matei D, Emerson RE, Lai YC, et al. Autocrine activation of PDGFRalpha promotes the progression of ovarian cancer. *Oncogene.* 2006;25:2060-2069.
- Buchdunger E, Zimmermann J, Mett H, et al. Selective inhibition of the platelet-derived growth factor signal transduction pathway by a protein-tyrosine kinase inhibitor of the 2-phenylaminopyrimidine class. *Proc Natl Acad Sci USA.* 1995;92:2558-2562.
- Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med.* 2001;344:1038-1042.
- Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002;347:472-480.
- Matei D, Kelich S, Cao L, et al. PDGF BB induces VEGF secretion in ovarian cancer. *Cancer Biol Ther.* 2007;6:1951-1959.
- Alberts DS, Liu PY, Wilczynski SP, et al. Phase II trial of imatinib mesylate in recurrent, biomarker positive, ovarian cancer (Southwest Oncology Group Protocol S0211). *Int J Gynecol Cancer.* 2007;17:784-788.
- Coleman RL, Broaddus RR, Bodurka DC, et al. Phase II trial of imatinib mesylate in patients with recurrent platinum- and taxane-resistant epithelial ovarian and primary peritoneal cancers. *Gynecol Oncol.* 2006;101:126-131.

30. Posadas EM, Kwitkowski V, Kotz HL, et al. A prospective analysis of imatinib-induced c-kit modulation in ovarian cancer: a phase II clinical study with proteomic profiling. *Cancer*. 2007;110:309-317.
31. Pietras K, Hanahan D. A multitargeted, metronomic, and maximum-tolerated dose "chemo-switch" regimen is antiangiogenic, producing objective responses and survival benefit in a mouse model of cancer. *J Clin Oncol*. 2005; 23:939-952.
32. Vlahovic G, Ponce AM, Rabbani Z, et al. Treatment with imatinib improves drug delivery and efficacy in NSCLC xenografts. *Br J Cancer*. 2007;97:735-740.
33. Mathew P, Fidler IJ, Logothetis CJ. Combination docetaxel and platelet-derived growth factor receptor inhibition with imatinib mesylate in prostate cancer. *Semin Oncol*. 2004; 31:24-29.
34. Cheng JQ, Godwin AK, Bellacosa A, et al. AKT2, a putative oncogene encoding a member of a subfamily of protein-serine/threonine kinases, is amplified in human ovarian carcinomas. *Proc Natl Acad Sci USA*. 1992;89: 9267-9271.
35. Cheng JQ, Jiang X, Fraser M, et al. Role of X-linked inhibitor of apoptosis protein in chemoresistance in ovarian cancer: possible involvement of the phosphoinositide-3 kinase/Akt pathway. *Drug Resist Updat*. 2002;5: 131-146.
36. Mathew P, Thall PF, Jones D, et al. Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: a modular phase I trial in androgen-independent prostate cancer. *J Clin Oncol*. 2004;22:3323-3329.
37. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-216.
38. Rustin GJ. Use of CA-125 to assess response to new agents in ovarian cancer trials. *J Clin Oncol*. 2003;21:187-193.
39. Le Page C, Koumakpayi IH, Alam-Fahmy M, et al. Expression and localisation of Akt-1, Akt-2 and Akt-3 correlate with clinical outcome of prostate cancer patients. *Br J Cancer*. 2006;94:1906-1912.
40. Kavanagh JJ, Kudelka AP, de Leon CG, et al. Phase II study of docetaxel in patients with epithelial ovarian carcinoma refractory to platinum. *Clin Cancer Res*. 1996;2:837-842.
41. Jayson GC, Parker GJ, Mullamitha S, et al. Blockade of platelet-derived growth factor receptor-beta by CDP860, a humanized, PEGylated di-Fab', leads to fluid accumulation and is associated with increased tumor vascularized volume. *J Clin Oncol*. 2005;23:973-981.
42. Tonary AM, Macdonald EA, Faught W, et al. Lack of expression of c-KIT in ovarian cancers is associated with poor prognosis. *Int J Cancer*. 2000;89:242-250.
43. Wilczynski SP, Chen YY, Chen W, et al. Expression and mutational analysis of tyrosine kinase receptors c-kit, PDGFRalpha, and PDGFRbeta in ovarian cancers. *Hum Pathol*. 2005;36:242-249.
44. Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2003;88:130-135.
45. Markman M, Zanotti K, Webster K, et al. Phase 2 trial of single agent docetaxel in platinum and paclitaxel-refractory ovarian cancer, fallopian tube cancer, and primary carcinoma of the peritoneum. *Gynecol Oncol*. 2003;91:573-576.
46. Verschraegen CE, Sittisomwong T, Kudelka AP, et al. Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma. *J Clin Oncol*. 2000;18:2733-2739.
47. Terauchi F, Hirano T, Taoka H, et al. Weekly docetaxel for patients with platinum/paclitaxel/irinotecan-resistant relapsed ovarian cancer: a phase I study. *Int J Clin Oncol*. 2003;8:348-351.
48. Tinker AV, GebSKI V, Fitzharris B, et al. Phase II trial of weekly docetaxel for patients with relapsed ovarian cancer who have previously received paclitaxel—ANZGOG 02-01. *Gynecol Oncol*. 2007;104:647-653.
49. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2007;351:1513-1520.
50. Fennelly D, Aghajanian C, Shapiro F, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol*. 1997; 15:187-192.
51. Markman M, Hall J, Spitz D, et al. Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. *J Clin Oncol*. 2002;20:2365-2369.
52. Helft PR, Daugherty CK. Are we taking without giving in return? The ethics of research-related biopsies and the benefits of clinical trial participation. *J Clin Oncol*. 2006;24: 4793-4795.