Original Articles

A phase 2 trial of oral imatinib in patients with epithelial ovarian, fallopian tube, or peritoneal carcinoma in second or greater remission

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Summary

Purpose of investigation: To determine the effect of imatinib on progression-free survival in patients with epithelial ovarian cancer in second or greater complete clinical remission (CCR). *Methods:* 35 patients were enrolled between 10/2002 and 1/2005. Eligible patients received imatinib at 400 mg daily orally. *Results:* One patient withdrew consent, and two patients received protocol therapy in first remission and were excluded. Five patients were removed for possibly related toxicity. No associations were seen between PDGF-R staining and PFS. *Conclusions:* Treatment with imatinib for patients with ovarian cancer in second CCR or greater did not prolong the PFS beyond the historical estimate.

Key words: Imatinib; Ovarian cancer; Peritoneal; Remission.

Introduction

Aggressive optimal surgical debulking and platinum with taxane therapy improved the median overall survival for patients with advanced ovarian cancer to in excess of five years in 2006, with the use of intraperitoneal treatment, but the long-term cure rate remains in the 20-30% range [1, 2]. Approximately 50% of patients will enter a pathologic first complete clinical remission, yet 90% of suboptimally debulked patients and 70% of optimally debulked patients relapse in 18-24 months. Subsequent and repeated chemotherapy responses are often seen with shortening intervals of disease control until broad chemotherapy resistance develops [3]. Opportunities to improve the outcome for patients exist by making primary therapy more effective, or by applying "consolidation" or "maintenance" approaches to patients in a complete primary or subsequent remission.

Numerous targets have been proposed for consolidation strategies. One such target, platelet-derived growth factor (PDGF), is produced by many cell types and mediates an autocrine transformation in responsive cells. It may also function in a paracrine fashion by stimulating angiogenesis, connective tissue and stromal development, and suppression of natural killer (NK) cells [4]. Normal human ovarian surface epithelial cells (HOSE) demonstrate a dose-dependent increase in [3H] thymidine incorporations when stimulated with PDGF in culture, and immunohistochemical analysis reveals that both PDGF-R-α and PDGF-β receptors are expressed [5]. There is also evidence that PDGF and PDGF-like molecules produced by ovarian cancer cells may be involved in paracrine stimulation of surrounding stroma. Cultured media with secreted PDGF-like molecules from malignant epithelial cell lines significantly stimulate the mitogenic activity of 3T3 fibroblasts [6].

PDGF is present by immunohistochemistry in 73-100% of human ovarian cell lines where no expression is noted in normal epithelial cells [7, 8]. PDGF-R is expressed in 36-81% of ovarian cancer tissues based on prior reports [5, 7, 9]. In this phase II study, we sought to determine whether inhibition of the PDGF-PDGF-R system could result in a decrease or delay in tumor recurrence among women in second or greater clinical remission. Our hypothesis was that remission prolongation might be achieved with imatinib by altering the autocrine transformation of ovarian epithelial cells, inhibiting the growth of residual malignant cells, and/or inhibiting stromal remodeling via the paracrine function.

Materials and Methods

Patient population, inclusions and exclusions

Eligible patients had 1) histologic confirmation of epithelial ovarian, primary peritoneal, or fallopian tube cancer at diagnosis; 2) initial surgical cytoreduction and chemotherapy with at least one platinum containing regimen; 3) failure of the primary regimen manifested by recurrent disease; and 4) were in a second or greater complete clinical remission following additional chemotherapy or surgery. Patients must have enrolled within 4.6 months of completing chemotherapy for recurrent disease. Complete clinical remission was defined as CA-125 < 35 U/ml, negative physical examination, and no definite evidence of disease by computed tomography (CT) imaging. Lymph nodes and/or soft tissue abnormalities < 1.0 cm are often

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present and were not considered definite evidence of disease. Patients must have had Karnofsky performance status (KPS) ≥ 60F and adequate organ function defined as absolute neutrophil count (ANC) ≥ 1,500/μl, platelet count ≥ 100,000/μl, total bilirubin and serum creatinine ≤ 1.5 times institutional upper limit of normal, and SGOT and alkaline phosphatase ≤ 2.5 times institutional upper limit of normal. Patients were excluded from the study if they had received any investigational drug or radiation therapy during the four weeks before study entry. Patients were also excluded if they had any uncontrolled cardiac, pulmonary, metabolic, renal, gastrointestinal or infectious diseases, the inability to take oral medications, or a history that placed the patient at an unacceptable risk for participation in the study. Therapeutic warfarin was not permitted.

The pretreatment evaluation included history and physical examination, assessment of KPS, complete blood cell count, hepatic function profile, serum creatinine, serum CA-125 level, ECG, and CT. During treatment, patients were evaluated monthly with physical examinations, and all laboratory studies were repeated. CT imaging was repeated every 12 weeks, or sooner at the discretion of the investigator if progression was suspected.

Treatment plan

Patients received imatinib orally daily continuously by taking four 100 mg tablets with food and a large glass of water. No dose interruptions or modifications were performed for grade 1 or 2 hematological toxicity. For grade 3 or 4 hematological toxicity defined as ANC < 1 X 10^9/l, or platelet count < 50 X 10^9/l, imatinib was held until toxicity resolved to ≤ grade 2, but no longer than two weeks or the patient was removed from the study. If grade 3 or 4 toxicity recurred after an interruption, the patient was removed from the study. Patients were also removed from the study for any other unacceptable ≥ grade 2 toxicity.

Immunohistochemistry studies

Representative slides of the primary malignancy were processed at our institution or by referring institutions (formalin-fixed paraffin-embedded), and were stained at Memorial Sloan-Kettering Cancer Center (MSKCC) via immunohistochemistry (IHC) for PDGF-R (commercial polyclonal assay, Santa Cruz, CA). PDGF-R α antibody (#SC-338) from Santa Cruz Biotechnology is a commercial rabbit polyclonal antibody raised against a peptide corresponding to amino acids 1065-1084 mapping within the carboxy terminal domain of PDGF-R. The antibody reacts with PDGF-R of mouse, rat, and human cell origin by Western blotting, immunoprecipitation and immunohistochemistry (data on file, Santa Cruz, Biotechnology). Standard immunoperoxidase techniques were used by the immunochemistry core facility at MSK as outlined in the laboratory procedures manual (revision 1995). Slides were reviewed by the investigating pathologists (RS and KP). Specimens were graded as 0-4 using a qualitative scale.

Study endpoints

The primary endpoint of the study was to determine the effect of imatinib therapy on progression-free survival (PFS). Treatment failure was defined based on the data from Rustin *et al.* [10] and was characterized by 1) physical examination evidence of tumor recurrence, 2) preferably radiographic evidence of disease recurrence using RECIST criteria, or 3) CA-125 elevation to twice the upper limits of normal (i.e., 70 U/ml), confirmed by a second sample, also > 70 U/ml. Patients were removed from the study at the time of treatment failure.

All patients provided written informed consent. The protocol was approved by the institutional review board and was reviewed annually.

Statistical considerations

The objective of this study was to estimate the median PFS among women in second or greater remission treated with oral imatinib as remission consolidation. PFS (protocol) was defined as the time from the protocol start date to progression, or last follow-up for the patients who did not progress; PFS intervals are reported in months. The first PFS (pre-protocol intervention) was measured as the time interval from the start of primary therapy to the date of first relapse (PFS1). The second PFS was measured as the interval from the start of secondary therapy to the date of the second relapse (PFS2). The third PFS was measured as the interval from the start of third therapy to the date of the third relapse (PFS3).

In the second or greater complete clinical remission group of patients, historically the median PFS2 is nine months. We planned to accrue 35 patients, at an accrual rate of three patients per month, with follow-up after accrual for an additional two years. A minimum follow-up of 18 months was required to enable us to estimate the median time to recurrence with a 95% confidence interval (CI) given by ± 4.5 months. This CI was computed under an exponential survival model. We would study the treatment further if we observed a median of more than 13.5 months.

Results

Patient characteristics

Thirty-five patients were enrolled in the study from October 2002 to January 2005. After initial enrollment, one patient withdrew consent prior to starting treatment.

Table 1. — *Patient characteristics (n = 32).*

Patient characteristics	Number	Range
Median age, (range)	53	25-72
Median KPS, (range)	90	80-100
Patient characteristics	**Number**	**%**
Disease site		
Ovarian	30	94
Peritoneal	2	6
Stage		
II	2	6
III	25	78
IV	3	9
Unstaged	2	6
Histologic Type		
Serous	22	69
Endometrioid	9	28
Clear cell	1	3
Grade		
1	1	3
2	6	19
3	25	78
Size of residual at primary debulking		
Optimal (≤ 1 cm)	22	69
Suboptimal (> 1 cm)	9	28
Unknown	1	3
2nd Remission	26	81
3rd Remission	6	19

KPS, Karnofsky performance status.

Two additional patients (6%) received imatinib in first clinical remission and were excluded from the analysis, leaving a total of 32 evaluable patients. Patient characteristics are detailed in Table 1. The median age was 53 years (range, 25-72 yrs) with median KPS of 90% (range, 80-100%). The majority of patients were Stage III (78%) or IV (9%) at diagnosis. Most patients (69%) were optimally debulked (≤ 1 cm residual disease) and the majority had papillary serous (69%) or endometrioid (28%) histology. All patients received taxane and platinum-based primary therapy. Thirteen (41%) patients underwent second-look assessment, and 21 (66%) received additional consolidation therapy after primary treatment. Eighteen (56%) of patients underwent a surgical procedure at the time of a recurrence. The majority of patients were enrolled on protocol in second complete remission (81%), with six patients (19%) receiving imatinib in the third remission. The median number of cycles of protocol therapy was three (range, 1-11). The median interval between the date of last chemotherapy and the start of protocol therapy was 1.7 months, ranging from 0.59-4.6 months.

Treatment toxicities

Two (5.9%) of 34 patients were removed from treatment owing to related toxicity (G 2 petechiae and G3 diarrhea), while 29 patients (85.3%) were removed for progression of disease. An additional three patients (8.8%) were removed from the study secondary to possibly related toxicity: pulmonary embolism (n = 1), elevated creatinine (n = 1), and ureteral calculi (n = 1). All five patients taken off the study for possible or definite related toxicity, were included in the analysis. Toxicities ≥ grade 3 not requiring removal from study were neutropenia (n = 3), thrombocytopenia (n = 1), and hyperglycemia (n = 1). The most frequent toxicities were grade 1 and 2 (Table 2).

Table 2. — *Treatment toxicities (n = 32).*

Adverse events	Grade			
	1	2	3	4
Neutropenia	12 (38%)	9 (28%)	3 (9%)	2 (6%)
Anemia	16 (50%)	8 (25%)	0	0
Thrombocytopenia	10 (31%)	0	1 (3%)	0
Hypokalemia	3 (9%)	0	0	0
Hypomagnesemia	1 (3%)	0	0	0
Hyperglycemia	9 (28%)	0	1 (3%)	0
Creatinine	3 (9%)	1 (3%)	0	0
Dry Eyes	2 (6%)	0	0	0
Abdominal pain	3 (9%)	0	0	0
Diarrhea	11 (34%)	1 (3%)	0	0
Nausea	10 (31%)	2 (6%)	0	0
Vomiting	3 (9%)	2 (6%)	0	0
Neuropathy	7 (22%)	0	0	0
Fatigue	12 (38%)	2 (6%)	0	0
Rash (cellulitis)	4 (12%)	1 (3%)	0	0
Petechia	0	1 (3%)	0	0
Other (ureteral calculi)	0	0	0	1 (3%)

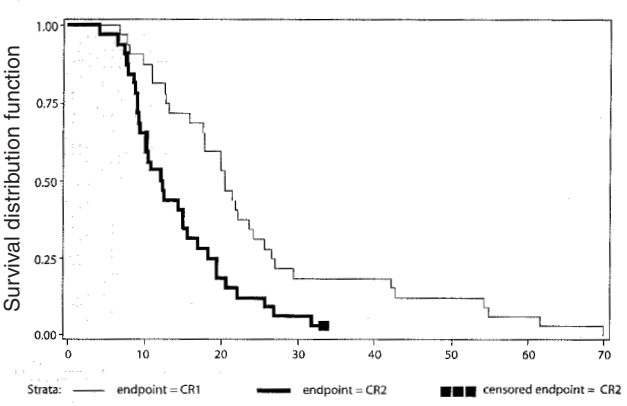

Figure 1. — Progression-free survival.
CR1: first clinical remission;
CR2: second clinical remission.

Primary treatment endpoint: progression-free survival

The PFS (PFS2) for patients receiving protocol therapy in second remission (n = 26) was 12.1 mos (95% CI, 9.1-15.1 mos) as seen in Table 3. The PFS (PFS3) for patients receiving protocol therapy in third remission (n = 6) was 15.9 mos (95% CI, 9.5-23.4 mos). The PFS from the start of protocol therapy or PFS (protocol) was 3.7 mos (95% CI, 2.7-5.8 mos).

The PFS (PFS 1) for all evaluable patients on protocol (pre-study intervention) was 20.4 mos (95% CI, 17.6-24.1 mos). The median time on treatment prior to initiation of imatinib therapy (i.e., time to return to complete clinical remission) for second remission patients was 4.8 mos (range, 0-32.8 mos). However, the median time on treatment for those patients receiving imatinib therapy in a third remission was 14.5 mos (range, 3.6-40.6 mos).

Table 3. — *Treatment outcome: duration of progression-free survival.*

Patients treated in PFS 2 or 3 (n = 32)	
PFS 1 (pre-protocol therapy)	20.4 mos (95% CI, 17.6-24.1 mos)
PFS 2	12.1 mos (95% CI, 9.4-15.5 mos)
PFS 3 (n = 9)	10.2 mos (95% CI, 9.5-23.4 mos)
Patients treated in PFS 2 only (n = 23)	
PFS 1	21.3 mos (95% CI, 17.8-25.6 mos)
PFS 2	12.3 mos (95% CI, 10.2-15.1 mos)

PFS, progression-free survival.

Table 4. — *Exploratory outcome: patients with PFS 2 > PFS 1 treated in PFS 2 (n = 6 of 26).*

Patient no.	Dur PFS 1	Dur PFS 2	Difference
2	26.5 mos	31.7 mos	5.2 mos
8	19.9 mos	20.6 mos	0.7 mos
14	7.96 mos	8.65 mos	0.6 mos
21	17.7 mos	26.8 mos	9.1 mos
28	10.9 mos	12.5 mos	1.6 mos

PFS, progression-free survival.

Table 5. — *Exploratory outcome: PFS2 rate at given time intervals.*

Time point (months)	PFS 1 (n = 32)	PFS 2 (n = 32)
3	100%	100%
6	100%	96%
9	90%	75%
12	81%	53%
15	71%	37%
18	59%	28%
21	46%	15%
24	34%	12%

PFS, progression-free survival.

Table 6. — *PDGF-R immunohistochemistry (n = 25).*

PDGF-R Score	Number of Patients	Percentage
0	14	56
1	5	20
2	3	12
3	3	12
4	0	0

PDGF, platelet-derived growth factor.

Exploratory endpoints

For patients receiving protocol therapy in second complete remission only (n = 26), six of 26 patients (23%) had PFS 2 > PFS1, with a median difference of 3.4 mos (range, 0.7-9.1 mos) as outlined in Table 4. Five of six (83%) of these patients with PFS2 > PFS 1 had complete surgical cytoreduction at recurrence followed by chemotherapy before protocol initiation.

Table 5 describes the patients receiving protocol therapy in CR2 or greater and remaining disease-free at given time points. The proportion of patients remaining in second remission among the 32 patients in second or greater CR versus time is as follows: 3 mos (100%), 6 mos (96%), 9 mos (745%), 12 mos (53%), 15 mos (37%), 18 mos (28%), 21 mos (15%) and 24 mos (12%). Figure 1 shows the PFS curves for all patients treated in CR2 or greater, and separately depicts the group treated in CR2.

PDGFR immunohistochemistry

Overall, 11 of 25 patients (44%) demonstrated some degree of PDGFR staining on a 0-4 scale, but only three patients (12%) scoring 3 or higher (Table 6). PDGFR data was missing in nine patients. No associations between PDGF staining scores and PFS were seen.

Discussion

There is much interest in investigating targeted consolidation or maintenance strategies for patients having ovarian cancer in both primary and secondary complete clinical remission. Preclinical studies have shown that c-kit and PDGFR may have a role in ovarian pathogenesis, and that their inhibition may prevent tumor growth [4, 5, 9, 11]. Imatinib is an oral tyrosine kinase inhibitor that demonstrates activity against PDGF-R, c-Kit, and Bcr-Abl [12].

This single-institution, open-label, phase II study examined PFS of patients with epithelial ovarian, fallopian tube, and primary peritoneal cancer in second or greater complete clinical remission who were treated with imatinib as consolidation therapy. In this study, the median PFS (PFS 2 or PFS 3) was 12.1 months. Progression-free survival (protocol) was relatively short (3.7 mos). The predetermined target of 13.5 months needed to consider this approach worthy of further study was not reached. Furthermore, over the range of PFS reported and recognizing the small sample size, there were no associations between PDGF expression and PFS.

During the reporting of our clinical trial, two other studies evaluating imatinib as treatment for measurable disease were reported and neither showed objective partial or complete responses. Coleman *et al.* [13] reported no objective clinical responses to imatinib in a phase II study of single-agent imatinib (600 mg daily) in 16 patients with recurrent platinum- and taxane-resistant epithelial ovarian and primary peritoneal carcinomas whose tumors expressed PDGF by immunohistochemistry. Stable disease was seen in four patients, including three patients with lack of disease progression greater than six months. More recently, Alberts *et al.* [14] reported the Southwest Oncology Group experience with 19 evaluable patients (2 positive for c-kit expression by IHC and 17 positive for PDGF-R expression by IHC) again showing no objective responses. Taken together, these two recently reported studies of imatinib in patients with measurable disease and our study for patients in remission demonstrate that meaningful activity of imatinib in patients with ovarian cancer is absent.

The target PFS from complete second clinical remission we selected as our endpoint is rarely separately reported in the literature in trials of recurrent disease. There is generally mention of the small subset of complete responders in each study, but little information about their specific characteristics and duration of remission. Therefore, making comparisons with historical data as we investigate more agents for consolidation is difficult if we rely on a PFS endpoint. Heterogeneous populations also provide possible confounding variables, including the number of chemotherapy or hormonal agents required to achieve remission, the duration of therapy, as well as treatment alterations based on changes in CA-125 or radiographic findings not meeting strictly defined RECIST definitions for progression of disease. The issue of a variable number of chemotherapy regimens required to return to remission (i.e., preprotocol therapy) is well illustrated in our study. The median duration of therapy was 4.8 months for second remission and 14.5 months for the six patients in third remission. It will clearly be important to limit the number of treatment regimens and cycles required to achieve remission in the design of future consolidation trials. This is particularly required if our endpoint is to prolong the standard definition of PFS 2 or 3, which is defined from the start of second- or third-line therapy to disease progression. Moreover, recent data have suggested that a simple deter-

mination of the median PFS may not be the most suitable endpoint by which to investigate consolidation approaches. Other suggested endpoints have included the proportion of patients having a second remission longer than the first [3] or patients continuously in remission at given time points [15].

In considering alternate endpoints, six of 26 (23%) of second complete remission patients in our study had a second remission longer than the first (23%) with four of them (11%) having potentially clinically meaningful differences (arbitrarily defined as > 1 month). This initially appears in contrast to the reported range of 3-8% in the literature [3]. However, five of six of these patients in our study had secondary complete surgical debulking at the time of their recurrence followed by chemotherapy. Secondary surgical cytoreduction in appropriate patients may prolong PFS, and thus the frequent use of secondary surgical cytoreduction for management of relapse may represent a confounding factor to exploring duration of second complete clinical remission as an endpoint for our patient group [16-18]. In future studies using PFS2 versus PFS1 duration endpoints, it will be important to define clinically significant differences in duration of PFS, as well as control for other variables such as secondary surgery. This endpoint, however, is still worthy of consideration as larger data sets of patients in remission are examined, and potential confounding factors can be understood.

Finally, based on the understanding that binary endpoints at fixed time points may avoid some inherent reporting biases [15], we reported the number of patients remaining in remission at a given time point. As large data sets of patients in remission are accumulated and analyzed, the goal of improving the percent of patients still in remission at a predetermined time point may be a useful outcome measure.

Conclusions

In summary, our study showed that imatinib given as consolidation treatment to women in second or greater complete remission did not prolong the expected median PFS, and is consistent with other trials showing no objective responses in patients with measurable disease. Future studies of consolidation in patients in remission could explore alternate endpoints including the use of the number of patients remaining in complete clinical remission at a given time point

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