Weekly Paclitaxel with Intermittent Imatinib Mesylate (Gleevec®): Tolerance and Activity in Recurrent Epithelial Ovarian Cancer

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Abstract. *Objective: Imatinib mesylate (IM, Gleevec), a potent PDGF/PDGFR tyrosine kinase inhibitor, affects stroma and vascular endothelial cells. Our study sought to determine the safety and activity of paclitaxel with an intermittent schedule of IM. Materials and Methods: rEOC patients previously treated with platinum/paclitaxel and ≤2 regimens for recurrence were enrolled. Paclitaxel 80 mg/m^2 was given on days 3, 10, 17 every 28 days and oral IM 300 mg bid on days 1-4, 8-11, and 13-18. Results: Between 2007-2009, 14 patients enrolled, 12 were evaluable. Nine patients were on study at 12 weeks. Objective responses (by RECIST and/or CA125) occurred in 4 patients. There were no grade 4, and only four grade 3 toxic events: diarrhea, edema and 2 cases of neutropenia. Early study closure was due to sufficient safety information with preliminary encouraging efficacy results. Conclusion: This weekly paclitaxel regimen with intermittent IM is tolerable with anti-tumor activity, making it suitable as part of future studies.*

Most patients with epithelial ovarian cancer (EOC) will relapse and undergo treatment with 'second-line' drugs, such as taxanes, topotecan, pegylated liposomal doxorubicin and/or gemcitabine (1). Greater understanding of the mechanisms of action and resistance pathways of these drugs may lead to more long-term control of disease.

Weekly administration of paclitaxel provides a pharmacologically-based continuous exposure that is more effective and less toxic than administration every three weeks (2-3). Inhibition of angiogenesis may contribute to the antitumor effects of paclitaxel beyond direct cytotoxicity (4-6).

Imatinib mesylate (IM, Gleevec®), a 2-phenylamino-pyrimidine derivative, is a selective inhibitor of ABL, c-KIT, and platelet-derived growth factor receptor (PDGFR) tyrosine kinases (7). Platelet-derived growth factor (PDGF) and its receptor have been implicated in the early transformation and sustaining of tumor growth, their associated vascular endothelium, and signaling between tumor and stroma (7, 8). Specifically, in ovarian cancer the relevance of PDGF and PDGFR signaling has been shown in tumor cell lines, orthotoptic models of peritoneal growth, and in specimens from patients (8-9). In addition, Henriksen *et al*. (10) noted their prognostic relevance: expression of PDGF was noted in 73% of ovarian carcinomas with 36% also expressing PDGFRα; expression of this receptor conferred a poor prognosis (10). Phosphorylation of PDGFR in tumor-associated endothelial cells further indicated that this pathway was active in ovarian carcinoma cells injected intraperitoneally in nude mice (8). These preclinical data led to the study of IM (11-13) as a single agent for ovarian cancer, revealing only hints of activity and some intolerance.

Nevertheless, there is an ongoing interest in investigating IM with paclitaxel by invoking several possible effects: (i) inhibition of PDGFR signaling in tumor stroma with reduction in the tumor interstitial fluid pressure (14), (ii) depolymerization of microtubules during the initiation of DNA synthesis and cell division (15), and (iii) blockade of PDGFR sensitizing rapidly dividing, genetically stable, tumor–associated endothelial cells to paclitaxel-induced apoptosis (8-9). Moreover, Shaked *et al*. (16) found that paclitaxel caused rapid circulating endothelial progenitor (CEP) mobilization (supporting proliferation of tumor cells);

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an effect that could be prevented by the co-administration of antivascular agents. A synergistic effect of IM's anti-angiogenic property with paclitaxel-induced apoptosis has been suggested by Apte *et al*. (8). Xenograft models using three human ovarian cancer cell lines, one of them paclitaxel-resistant, implanted into the peritoneal cavity of nude mice showed that daily oral administrations of STI571 (IM) with weekly intraperitoneal injections of paclitaxel produced significant therapeutic effects in all three cell lines, mediated in part by the induction of apoptosis in tumor-associated endothelial cells. Administration of small repeated doses of paclitaxel given with antivascular agents may be the optimal schedule for such additive effects.

Following these compelling laboratory and clinical leads, a phase II trial was planned in recurrent EOC utilizing weekly paclitaxel given together with oral intermittent IM. We utilized a dose and schedule from a phase I study (17), updated verbally by the senior author (J. Marshall), to test out the safety and efficacy of such combination in patients with recurrent ovarian cancer. Our hypothesis was that this combined treatment would be tolerable and improve on the efficacy of paclitaxel – a drug known to be effective in this setting.

Materials and Methods

Patients. From May 2007 to August 2009, fourteen patients were enrolled in this study. Patients with recurrent or persistent histologically confirmed, epithelial ovarian, fallopian tube or primary peritoneal carcinoma (of any stage or grade at diagnosis) following initial cytoreductive surgery and at least one platinum and taxane-based chemotherapy regimen and not more than two subsequent regimens were eligible to take part in this study. All patients were ≥18 years, had ECOG performance status ≤2, normal pre-treatment complete blood count (CBC) and adequate renal and liver function tests (serum creatinine <1.5 × upper limits of normal (ULN), serum total bilirubin <1.5 × ULN, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) <2.5 × ULN).

Exclusion factors. These included chemotherapy treatment within 21 days of study drug, prior radiotherapy to ≥25% of the bone marrow, presence of brain metastasis, unstable cardiac disease, severe and/or uncontrolled medical disease, need for chronic treatment with oral anticoagulants or intake of any drug that interfered with IM metabolism (*e.g*., warfarin, other major CYP450 substrates). Surgery within 2 weeks prior to study entry, and a history of non-compliance also excluded the patient.

This single institution open label phase II clinical trial was approved and monitored by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of New York University. All participants provided a written voluntary informed consent prior to enrollment.

Treatment plan and modifications. IM orally was given at a dose of 300 mg twice daily for 4 consecutive days every 7 days (four days on, three days off, beginning on day 2 prior to beginning weekly paclitaxel 80 mg/m^2 intravenously (*i.v.*) over 1 hour on days 3, 10 and 17 of each 28-day cycle. Premedication consisted of dexamethasone 20 mg *i.v.* (reduced in subsequent cycles), diphenhydramine 50 mg *i.v.*, and cimetidine 300 mg *i.v.* or ranitidine 50 mg *i.v*. Dose reduction of paclitaxel by 25% was carried out for persistent neuropathy exceeding grade 1. IM was reduced by 50% for non-hematologic toxicity clearly related to this agent. Study treatment was to be terminated for any non-hematologic toxicity exceeding grade 2 for longer than 2 weeks. Paclitaxel and IM were withheld for absolute neutrophil counts <500 and/or platelets <50,000 until the toxicity had resolved to <grade 2.

Table I. *Demographics of enrolled patients (n=14).*

Characteristic	N (% or range)
Total number of patients	14
Median age at diagnosis (years)	54 (44-70)
Performance status (ECOG)	0 (0-2) *
Primary tumor	
Ovarian	9 (64.3)
Fallopian tube	2 (14.3)
Primary peritoneal	3 (21.4)
Histology	
Papillary serous	10 (71.4)
Endometrioid	2 (14.3)
Clear cell	2 (14.3)
Initial stage	
Ic	2 (14.3)
IIIc	10 (71.4)
IV	2 (14.3)
Median number of prior chemotherapy regimens	3 (1-8)**

*Mode was 0; PS was 2 in only two patients; **2 patients exceeding 3 regimens were protocol violations.

Study parameters and method of evaluation. Response and progression were evaluated in this study according to Response Evaluation Criteria in Solid Tumors (RECIST) (18). Patients were evaluated for clinical response (complete or partial) by computed tomographic (CT) scan at baseline and every 12 weeks, or by CA-125 every 4 weeks (19).

Progression-free survival (PFS) was calculated from the beginning of the treatment to progression, death or end of study, whichever occurred earlier. Adverse events were evaluated according to NIH Common Toxicity Criteria v2 (20).

Statistical considerations. The primary endpoint was response rate at 12 weeks according to the RECIST criteria. Secondary endpoints were the percentage of patients that continued on treatment with no progression at 12 weeks, and PFS. A sample size of 50 patients was calculated to achieve 80% power to detect an increase in PFS at 12 weeks, from 50% in patients on paclitaxel alone to 68% in patients on both paclitaxel and IM (one-sided test, with target significance level of 95%).

Results

Demographic characteristics of the patients are shown in Table I.

Table II. *Treated patients (n=12): individual characteristics and results.*

Patient	Age at enrollment (years)	Platinum sensitivity (at time of enrollment)	PFI prior to entry (months)	Number of previous regimens	Objective response	Number of cycles	PFS (months)	OS (months)
01	69	Resistant	2	8*	SD	7	7.0	7.3+
02	60	Sensitive	8.4	1	PR	12.3	12.6	25.5+
03	65	Resistant	0	3	PR	11	11.4	11.7+
04	47	Sensitive	13.4	3	PR	5.3	5.4	16.1
05	54	Resistant	0	3	PD	2.7	2.7	9.4
06	60	Resistant	2	2	SD	12.3	12.6	33.4+
07	76	Resistant	0	4*	PD	4	3.6	29.0+
08	67	Resistant	0	3	PR	4.3	4.4	25.2+
09	57	Resistant	2	3	PD	6	5.8	6.1+
10	59	Resistant	0	3	SD	7	7.2	7.2
11	56	Resistant	2	3	PD	2	1.7	22.6+
12	57	Resistant	2	2	PD	<1	<1	4.1

PFI, Platinum-free interval; PFS, progression-free survival; OS, overall survival (+ patients that are alive); *protocol deviations in eligibility criteria (exceeded prior treatment regimens); SD, stable disease; PR, partial response; PD, progressive disease.

The median age at enrollment was 58 years (range 46-76) and twelve patients had an ECOG performance status (PS) of 0 to 1, with 2 patients with a PS of 2. All were experiencing disease progression after being exposed to a median of three prior regimens.

Only 12 were evaluable of 14 enrolled since 2 patients never received treatment because of rapid symptomatic deterioration. Only two of the patients were still potentially sensitive to platinums. Of the 12 evaluable patients, 1 went off study after 4 weeks because of shortness of breath, headache and periorbital edema (probably treatment related); and 2 had symptomatic progression of disease after 1 and 11 weeks of treatment, respectively (Table II). With a median follow-up of 18 months (range 3-33+ months), all patients are now off study. Nine out of 12 patients were progression free and on treatment at 12 weeks. Partial response (PR) was observed in 4 patients (2 confirmed by RECIST criteria and 2 by CA-125 criteria (19). A platinum-resistant patient with an endometrioid ovarian tumor (#3) who had a PR by RECIST and CA-125 met both of these criteria only after 6 cycles, with eventual progression after 12.6 months. All other responders had papillary serous cancer; 1 patient with clear cell carcinoma and hypercalcemia did not respond. Stable disease (SD) was reported in 3 patients and progression of disease (PD) in 4. PFS longer than 6 months was observed in 5 patients, and PFS longer than 12 months in 2 patients.

Toxicities are shown in Table III. No toxicity-related deaths were reported. Grade 3-4 non-hematological toxicities were rare: one patient had grade 3 diarrhea after the initial cycle and it did not recur after reduction of IM dose to 300 mg/day for all subsequent cycles. Another patient required 25% reduction of paclitaxel dose for the next three cycles after an episode of grade 3 neutropenia. Both IM and paclitaxel doses were reduced by 25% in one patient with neutropenia and thrombocytopenia grade 3 after 11 cycles of treatment.

Table III. *Treated patients (n=12): Toxicity.*

Toxicity	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematological				
Anemia*	4 (33)	5 (41)	2 (17)	-
Neutropenia	3 (25)**	2 (17)	2 (17)	-
Thrombocytopenia	1 (8)	-	1 (8)	-
Non-hematological				
Nausea	6 (50)	4 (33)	-	-
Vomiting	4 (33)	1 (8)	-	-
Fatigue	7 (68)	2 (17)	-	-
Diarrhea	4 (33)	1 (8)	1 (8)	-
Neuropathy	7 (68)	-	-	-
Skin toxicity	1 (8)	1 (8)	-	-
Alopecia	5 (41)	-	-	-
Mucositis	1 (9)	-	-	-
Myalgia	3 (25)	-	-	-
Edema	1 (8)	1 (8)	-	-
Shortness of breath	-	1 (8)	-	-
Palpitation	4 (33)	-	-	-
Headache	-	1 (8)	-	-

*Including grade 1 (2) and grade 2 (1) anemia at baseline; **one complicated by fever. Premature closure of this trial was due to initial slow accrual and the realization that response rates were not an adequate endpoint.

Discussion

Weekly paclitaxel in the salvage setting of recurrent EOC (3, 21) has shown a superior toxicity profile with similar efficacy when compared with the standard 3-weekly schedule. In a recent phase III study performed in Japan (22), the weekly schedule yielded a significantly better PFS and survival compared to the conventional induction every 3-week schedule, and it is currently being studied by the Gynecologic Oncology Group [GOG0252] (23). Additionally, paclitaxel is active in the presence of platinum resistance (24). Potentiation of its antitumor activity through anti-angiogenic or other effects is desirable, and the tyrosine kinase inhibitor, IM, was a logical candidate for trial, despite failing to show independent anti-tumor activity against ovarian cancer as a single agent. When given prior to paclitaxel, preclinical studies suggested that IM could enhance its anti-tumor effects, and a tolerable combination was developed in a phase I study (17).

This study demonstrates the feasibility of combining paclitaxel with intermittent IM. The regimen yielded only mild to moderate toxicities and yet showed appreciable anti-tumor effects. The combination met the prespecified secondary endpoint to exceed a median of 50% of patients free of disease progression and on study at 12 weeks. In fact, 5 of the 12 treated patients had a PFS of more than 6 months and 2 of the 12 more than 12 months. Side effects attributed to IM resulted in only one dose modification, and were not cumulative, in striking contrast with continuous schedules. With the findings noted, it is concluded that the intermittent dose-schedule of IM with weekly paclitaxel is tolerable over several cycles, and that the activity observed was sufficient to warrant further investigation in recurrent ovarian cancer.

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