Phase I trial of docetaxel and thalidomide: a regimen based on metronomic therapeutic principles

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Summary Purpose: Pre-clinical models have demonstrated the benefit of metronomic schedules of cytotoxic chemotherapy combined with anti-angiogenic compounds. This trial was undertaken to determine the toxicity of a low dose regimen using docetaxel and thalidomide. **Patients and Methods:** Patients with advanced solid tumors were enrolled. Thalidomide 100mg twice daily was given with escalating doses of docetaxel from 10 to 30mg/m²/week. One cycle consisted of 12 consecutive weeks of therapy. The maximal tolerated dose (MTD) was defined as the dose of thalidomide along with docetaxel that caused ≤grade 1 non-hematologic or ≤grade 2 hematologic toxicity for cycle one. **Results:** Twenty-six patients were enrolled. Dose-limiting toxicities (DLTs) were bradycardia, fatigue, fever, hyperbilirubinemia, leukopenia, myocardial infarction, and neutropenia. Prolonged freedom from disease progression was observed in 44.4% of the evaluable patients. **Conclusions:** This anti-angiogenic regimen was well tolerated and demonstrated clinical benefit. The recommended phase II dosing schedule is thalidomide 100mg twice daily with docetaxel 25mg/m²/week.

Keywords Metronomic · Docetaxel · Thalidomide · Angiogenesis · Phase I

Introduction

In 1971 Folkman proposed that tumors lay dormant *in situ* for months to years, rarely growing beyond 2–3mm³ in maximum size until the development of neovascularization [1]. When a tumor becomes vascularized, a subgroup of cells “switches” to an angiogenic phenotype with the emergence of markedly increased tumor growth, tumor cell invasion, and ultimately dissemination [2–4]. The combination of anti-angiogenesis inhibitors to cytotoxic chemotherapy can actually increase drug delivery to the tumor by normalizing the aberrant tumor vascular structure, decreasing vessel density, and decreasing tumor interstitial pressure [3, 5–8]. The inhibition of tumor angiogenesis can be achieved using conventional chemotherapeutic agents by damaging rapidly dividing endothelial cells that supply tumor blood vessels, in contrast to the mature quiescent endothelial cells in non-cancerous tissues [9].

Pre-clinical models demonstrating the synergy of combined metronomic chemotherapy (low doses given continuously or frequently without extended breaks) with an angiogenesis inhibitor set the stage for our trial [10]. Klement et al. [11] demonstrated that a combination of vinblastine plus an anti-vascular endothelial growth factor agent resulted in prolonged regression of established tumors, without any host toxicity, for greater than six months of therapy Browder et al. [12] reported a metronomic schedule of cytotoxic chemotherapy with an anti-angiogenic agent in a cyclophosphamide resistant Lewis lung cancer model. This combination produced sustained eradication of tumor

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growth superior to the conventional high dose cyclophosphamide schedule. Browder also demonstrated that apoptosis of tumor vascular endothelium preceded apoptosis of drug-resistant tumor cells using the metronomic schedule. Thus by targeting the genetically stable tumor vascular endothelium with a cytotoxic agent plus an anti-angiogenic compound, this regimen could cause primary tumor vascular damage resulting in secondary tumor cell death.

Our study attempted to emulate the pre-clinical data using low dose chronic cytotoxic chemotherapy in combination with an anti-angiogenic agent in hopes to achieve a more pronounced anti-angiogenic effect than cytotoxic effect with minimal toxicity in solid tumors. These chronic schedules may allow for prolonged plasma concentration levels without inducing any significant drug-related clinical toxicity. Docetaxel was selected as the cytotoxic agent because of the pre-clinical data demonstrating that microtubule stabilizing agents can inhibit endothelial cell proliferation, motility, and invasiveness in a dose-dependent manner [13, 14]. Weekly docetaxel has minimal toxicity and has activity in solid tumor malignancies [15]. Certain growth factors can inhibit the anti-angiogenic effects of docetaxel, which can be overcome with the addition of an anti-angiogenic agent [16, 17]. Thalidomide, which is generally well tolerated at low dose chronic administration, also inhibits angiogenesis [6, 18, 19]. This phase I study evaluated the toxicity, and secondarily the clinical benefit, of a metronomic regimen of docetaxel and thalidomide for patients with advanced solid tumors.

Materials and methods

Patient eligibility

Patients with histologically confirmed solid tumors not amenable to standard therapy were eligible. Other inclusion criteria included age ≥ 18 years, life expectancy of at least

four months, ECOG performance status 0 or 1, and measurable or evaluable disease. At least four weeks must have elapsed since prior large-field radiation therapy. Patients must have discontinued previous anti-cancer therapy for at least three weeks and recovered from all treatment-related toxicity. Peripheral neuropathy had to be less than or equal to grade 1 prior to study enrollment. Sexually active patients were required to use contraception, patients had to comply with the FDA-mandated thalidomide STEPS program, and women of child-bearing age had to have a negative pregnancy test. Exclusion criteria included white blood cell count $< 4,000/\mu\text{l}$ or ANC $< 1,500/\mu\text{l}$, platelets $< 100,000/\mu\text{l}$, hemoglobin $< 10\text{gm/dL}$, impaired hepatic function (total bilirubin $>$ upper limit of normal [ULN], transaminases $> 2.5 \times \text{ULN}$ if alkaline phosphatase was $< \text{ULN}$, or alkaline phosphatase up to $4 \times \text{ULN}$ if transaminases were normal), renal dysfunction (creatinine $> 1.5\text{mg/dl}$ or creatinine clearance $< 60\text{ml/min/1.73m}^2$), New York Heart Association classification III or IV heart disease, pregnant or lactating patients, and patients with a history of a hypersensitivity reaction to docetaxel. Patients with a prior exposure to thalidomide and docetaxel were allowed to enroll. The study was carried out with ethical approval and patients' written informed consent. The protocol adhered to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan, in accordance with National Cancer Institute regulations.

Treatment plan

The goal of this trial was to identify the maximal tolerated doses (MTDs) of thalidomide given twice daily with weekly docetaxel. Patients were enrolled in cohorts of three and expanded to six if dose-limiting toxicities (DLTs) occurred (see Table 1). No intra-patient dose escalation was allowed. Thalidomide 100mg twice daily was given with escalating weekly doses of docetaxel from $10\text{mg/m}^2/\text{week}$

Table 1 Dose escalation of patient cohorts and dose-limiting toxicities

Dose Level	Number of Patients	Thalidomide Twice Daily	Docetaxel $\text{mg/m}^2/\text{week}$	Dose-limiting Toxicities
1	4 ^a	100	10	None
2	3	100	20	None
3	6	100	25	Grade 3 hyperbilirubinemia
4	4 ^b	100	30	Grade 3 (fatigue, fever, leukopenia) Grade 4 (cardiac event, neutropenia)
5	4 ^c	150	20	None
6	5	150	25	Grade 3 (bradycardia, fatigue)

^a Patients replaced for docetaxel hypersensitivity

^b Patients replaced for progressive disease before receiving combination therapy

^c Patients replaced for allergic rash

to 30mg/m²/week. Once the MTD of thalidomide 100mg twice daily was achieved, the thalidomide dose was increased to 150mg twice daily given with a lower dose of docetaxel. The docetaxel was then increased in each subsequent cohort until the MTD of thalidomide 150mg twice daily with weekly docetaxel was reached. Due to the possible thromboembolic potential of this drug combination, warfarin 2mg daily was given as prophylaxis. Bisacodyl 10mg orally daily was given to prevent thalidomide-induced constipation. Diuretics were allowed for edema or fluid retention. All drugs were given continuously for 84days (12weeks), which constituted one treatment cycle. Patients had to complete one full cycle in order to be fully evaluable for toxicity endpoints.

The MTD was defined as the maximum dose of thalidomide in combination with docetaxel that caused $\leq$ grade 1 non-hematologic or $\leq$ grade 2 hematologic toxicity for cycle one. The DLT was defined as the dose at which one out of three patients (or two out of six patients in the expanded cohort) experienced any drug-related $\geq$ grade 2 non-hematologic or $\geq$ grade 3 hematologic toxicity. Exceptions to this included grade 2 sedation (but not fatigue), grade 2 alopecia, untreated grade 2 nausea and constipation, hypersensitivity reactions to docetaxel (grade 4 events required treatment discontinuation), and non-life threatening thromboembolic events (except for pulmonary embolism which was considered a DLT). Therefore, the MTD was the next lower dose than the DLT.

Toxicity and response evaluation

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Baseline evaluation included a physical exam, ECOG performance status, tumor measurements, clinical staging, laboratory tests (complete blood count with differential, serum chemistry, and liver function tests), and serum pregnancy test. Physical exam and performance status were assessed on day one of each cycle, every four weeks, and at the completion of the study. Tumor measurements were done prior to cycle one, at the end of each cycle, and at the completion of the study. Laboratory testing was done weekly throughout the study starting on day one of each cycle and at study completion. Serum pregnancy tests were done within 24h prior to initiating thalidomide, every week during the first four weeks of treatment, then every four weeks in the case of regular menstrual cycles or every two weeks if cycles were irregular. Disease response and progression were evaluated by the RECIST criteria [20].

Dose modification and weekly treatment guidelines

During cycle one, ANC $\leq$ 1,000/ μ l and platelets $\leq$ 50,000/ μ l were considered DLTs. However, during cycle two and

beyond, two separate one-week delays were allowed for count recovery; otherwise patients were removed from the study. Dose modification of thalidomide was allowed for $\geq$ grade 2 sedation. For cycle two and beyond, docetaxel was dose reduced by 25% for grade 2 neuropathy and discontinued for grade 3 or 4 neuropathy. Two dose reductions of docetaxel were allowed for hepatic dysfunction. Each cycle lasted 12weeks (84days), and missed doses were not made up. Patients were removed from the study at the time of disease progression.

Statistical analysis

Patients were enrolled in cohorts of three, or six in an expanded cohort. Thus for each MTD, common toxicities (occurring in $\geq$ 30% of patients) would rarely be unobserved ($p = 0.11$), and very common toxicities (occurring in 50% of patients) would almost never be missed.

Table 2 Patient characteristics

Characteristics	Number of patients
Total	26
Assessable for response	18
Assessable for toxicity	22
Age (years)	
Median	53
Range	31–78
Sex	
Male	14
Female	12
Ethnicity	
White	22
Black or African-American	2
Hispanic or Latino	1
Asian	1
Performance status	
ECOG 0	13
ECOG 1	13
Prior surgery	17
Prior radiation	12
Number of prior systemic therapy regimens	
0–1	6
2–3	16
$\geq$ 4	4
Tumor types	
Prostate	4
Melanoma	3
Renal cell carcinoma	3
Lung	2
Other ^a	14

^a Other tumor types included ampullary, breast, carcinoid, cholangio-carcinoma, colon, esophageal, gastric, gastro-intestinal stromal tumor, head and neck, pancreatic, sarcoma, thymoma, thyroid, and transitional cell carcinoma of the ureter (one patient each)

Results

Patient characteristics

Patients were enrolled from August 2002 to November 2004, and the study was completed in February 2005. A total of 26 patients were enrolled (see Table 2). Eight patients were not evaluable for response secondary to early removal from the study due to docetaxel reaction (3), rapidly progressive disease (3), dose-limiting rash (1), and dose-limiting fatigue plus myocardial infarction (1). Two patients with progressive disease who were on-study for 34 and 51 days, as well as the patients with the above DLTs, were used for toxicity data. The other patient with progressive disease who was on study for only 17 days was omitted from the safety data. Twelve patients had prior radiotherapy, and all but one patient received prior systemic chemotherapy or hormonal therapy. The median number of prior systemic regimens was two (range zero to six). The most common tumor types on the study were prostate (4), melanoma (3), renal cell (3), and lung (2). The median time on treatment was 99 days (range 17 to 332 days). Seven patients received more than one cycle.

Toxicity

Overall this metronomic 12-week schedule was well tolerated. Table 3 lists the toxicities observed in cycle one. Common grade 1 or 2 toxicities included alopecia, anemia, constipation, dizziness, dyspnea, fatigue, hyperglycemia, hypoalbuminemia, hypocalcemia, and hyponatremia. There were no bleeding events during the entire trial for all cycles. There was one thromboembolic event consisting of non-ST elevation myocardial infarction which was dose-limiting. The patient fully recovered from this event.

At the dose levels of thalidomide 100mg twice daily with weekly docetaxel 10mg/m² and 20mg/m², seven patients were enrolled (see Table 1). One patient was not evaluable because of docetaxel hypersensitivity. There were no DLTs observed in the other six patients. At the dose level of thalidomide 100mg twice daily with docetaxel 25mg/m²/week, the only DLT in the six patients was one episode of grade 3 hyperbilirubinemia, which occurred in a patient with rapidly progressive disease. DLTs were observed in two of the four patients at the thalidomide 100mg twice daily and docetaxel 30mg/m²/week cohort. These toxicities consisted of grade 3 fatigue, fever, and leukopenia, as well as grade 4 neutropenia and acute myocardial infarction. Therefore, the MTD was determined to be thalidomide 100mg twice daily with docetaxel 25mg/m²/week.

In a new cohort, thalidomide was then dose escalated to 150mg twice daily with docetaxel 20mg/m²/week. One patient was replaced for a grade 3 rash, and the other three

Table 3 Toxicity during cycle one

	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	10			
Alt/Ast elevation	8			
Anemia	8	4	1	
Anorexia	6			
Bicarbonate abnormality	6			
Bradycardia			1 ^a	
Constipation	5	7		
Cardiovascular				1 ^a
Dizziness	12			
Dyspnea		8	1	
Edema	3			
Fatigue	7	6	3 ^a	
Fever	3		1 ^a	
Hot flashes	4			
Hyperbilirubinemia			1 ^a	
Hyperglycemia	7	5		
Hypoalbuminemia	11	4		
Hypocalcemia	8	4		
Hypoglycemia	3			
Hypomagnesemia	6			
Hyponatremia	12			
Hypophosphatemia			2	
Insomnia	7			
Leukopenia	3	5	1 ^a	
Lymphopenia		4	9	
Mood change	3			
Mucositis	5			
Nausea	7			
Neuropathy	6			
Neutropenia				1
Night sweats	3			
Ocular disturbances	5			
Pain	5	3		
Rash	8		1 ^a	
Taste disturbance	4			
Thrombocytopenia	4			
Transfusion requirement			2	
Vomiting	6			
Weight loss	3			

Table includes all grade 3 or 4 toxicities. Grade 1 or 2 toxicities occurring in less than 10% of the patients are excluded

^a Signifies a dose-limiting toxicity

patients at this dose level did not experienced DLTs. In the next cohort, patients were given thalidomide 150mg twice daily with docetaxel 25mg/m²/week. Five patients were dosed at this level, but there were two grade 3 DLTs of bradycardia and fatigue. Therefore, further dose escalations with thalidomide 150mg twice daily were not performed. Since it was unlikely that any significant clinical difference existed between thalidomide 100mg twice daily with docetaxel 25mg/m²/week and the thalidomide 150mg twice

daily with docetaxel 20mg/m²/week, the trial was closed to accrual. Therefore the recommended phase II dose is thalidomide 100mg twice daily with docetaxel 25mg/m²/week for 12 consecutive weeks of therapy.

Seven patients (27%) completed more than one cycle. In cycle two and beyond there was one grade 4 toxicity of neutropenia, grade 3 toxicities of lymphopenia (three patients) and dyspnea (two patients), as well as grade 3 anemia requiring transfusion, fatigue, leukopenia, syncope, and weight gain (one patient each). Dose reductions of thalidomide beyond cycle one were for bradycardia and somnolence (two patients each), as well as for fatigue, neutropenia, rash, and syncope. Docetaxel was dose reduced after cycle one for anemia, neuropathy, and thrombocytopenia.

Anti-tumor activity

Twenty-six patients were enrolled, but only 18 completed one cycle (84days) of therapy. Four patients were not evaluable for response because of docetaxel hypersensitivity (3) and dose-limiting rash (1). Three patients were not able to complete the 84-day cycle due to progressive disease. One patient was removed from study prior to cycle one response evaluation secondary to dose-limiting fatigue and myocardial infarction. Of these 18 patients that completed cycle one, the median number of days on trial was 106 (range 85 to 334days). Clinical benefit, as defined by either a partial response or stable disease, was observed at all dose levels except the thalidomide 150mg twice daily with docetaxel 25mg/m²/week (see Table 4). One patient with non-small cell lung cancer had a partial response, and eight patients experienced stable disease with tumor types of prostate (3), melanoma (2), and one each of papillary thyroid, gastric, and carcinoid. Three out of four prostate cancer patients had reductions in their PSA ranging from 44 to 76%.

Discussion

The therapeutic objective for a metronomic anti-cancer schedule is maximum efficacy with minimum toxicity. This is somewhat different from the chemotherapy regimens over the last 25 years which consisted of giving the MTDs of drugs every three to four weeks at the expense of toxicities by targeting the tumor cells at the expense of normal tissue. Unfortunately, the genetically unstable tumor cell can rapidly develop resistance to these cytotoxic agents. Thus, although initial tumor responses are commonly seen using such therapies, eventual tumor growth and dissemination is frequent. A different anti-cancer approach is to target the tumor vascular endothelium. By targeting the genetically stable endothelial cells, there is less risk of selection for drug-resistance [4, 21, 22]. As the pre-clinical work of Klement and Browder demonstrated, the primary effect of anti-angiogenesis is apoptosis of the vascular endothelium [11, 12]. Secondary effects are decreasing the tumor blood supply and inhibiting tumor growth. Our trial modeled this pre-clinical work by developing a metronomic chronic schedule using low dose docetaxel and thalidomide to achieve clinical benefit without inducing significant drug-related toxicity.

Combinations of cytotoxic agents and angiogenesis inhibitors have shown anti-tumor effects in pre-clinical studies [23–31]. The novelty of our study combines metronomic chemotherapy with an anti-angiogenic agent in the clinical setting. There are few published clinical trials using such a combination, mostly phase I–II or abstracts [32–39]. In contrast to our study which showed benefit of docetaxel with thalidomide in solid tumors, Colleoni found that the addition of thalidomide to metronomic chemotherapy in advanced breast cancer patients did not improve the response rate compared to chemotherapy alone [40]. However, other studies showed favorable results with

Table 4 Patients with a partial response or stable disease

Patient number	Cohort	Best response	Tumor type	Study duration (days)
3	1 ^a	Stable disease	Melanoma	332
5	2 ^b	Partial response	Non-small cell lung	334
6	2	Stable disease	Prostate	293
7	2	Stable disease	Papillary thyroid	185
12	3 ^c	Stable disease	Prostate	246
14	4 ^d	Stable disease	Melanoma	141
16	4	Stable disease	Gastric	99
19	5 ^e	Stable disease	Prostate	168
20	5	Stable disease	Carcinoid	141

^a Cohort 1: Thalidomide 100 mg twice daily + docetaxel 10 mg/m²/week for 12 weeks

^b Cohort 2: Thalidomide 100 mg twice daily + docetaxel 20 mg/m²/week for 12 weeks

^c Cohort 3: Thalidomide 100 mg twice daily + docetaxel 25 mg/m²/week for 12 weeks

^d Cohort 4: Thalidomide 150 mg twice daily + docetaxel 30 mg/m²/week for 12 weeks

^e Cohort 5: Thalidomide 150 mg twice daily + docetaxel 20 mg/m²/week for 12 weeks

combination metronomic chemotherapy and thalidomide in malignancies [41–43].

Few trials have evaluated the docetaxel and thalidomide combination, although with slightly different dosing than in our trial. A phase II trial of docetaxel 30 mg/m²/week for three weeks with or without thalidomide 200 mg daily in 75 patients with androgen-independent prostate cancer showed a significantly higher response rate and overall survival with the combination therapy [44, 45]. Thromboembolic events occurred in 18% of patients on the combination arm as opposed to 0% of patients on the docetaxel alone arm; with the addition of thrombosis prophylaxis, no further events occurred [44]. Of note, all patients with a history of thromboembolic events were randomized to the thalidomide arm [46]. Only one patient in our study experienced a thromboembolic event, despite the use of prophylactic warfarin. The combination of docetaxel and thalidomide has also been associated with pulmonary toxicity including pleural and pericardial effusions, dyspnea on exertion, interstitial lung disease, and pulmonary embolism [44, 47]. Only one grade 3 dyspnea occurred in our study, but grade 2 dyspnea was frequent. Otherwise, no other pulmonary toxicity was seen. Compared to Dahut's docetaxel/thalidomide arm [44], we had notably less diarrhea, dry mouth, edema, neuropathy, neutropenia, and severe hyperglycemia. Our patient group had more mild anemia, hyperglycemia, thrombocytopenia, and transaminitis. Both studies shared constipation, dizziness, fatigue, nausea, vomiting, ocular symptoms, pain, and rash as common side effects. More than half of our patients had hypoalbuminemia, hypocalcemia, hyponatremia, and lymphopenia, which was not reported by Dahut.

This trial utilized prolonged drug administration over 12 weeks. Therefore, certain grade 1–2 side effects were considered DLTs as this regimen was meant to be manageable throughout a chronic schedule. Overall this regimen was very well tolerated, and the only severe myelosuppressive event was one episode of grade 4 neutropenia. One patient had a grade 4 cardiac episode and recovered without any further cardiac events. This was the only thromboembolic event in our study. In prior studies, thromboembolic events occurred in 28% patients treated with thalidomide and chemotherapy without prophylaxis [48]. Significant toxicity was seen at dose level thalidomide 150 mg twice daily with docetaxel 25 mg/m²/week. Therefore, further dose escalation with thalidomide 150 mg twice daily was not performed. Given the low likelihood of significant clinical difference between thalidomide 100 mg twice daily with docetaxel 25 mg/m²/week and thalidomide 150 mg twice daily with docetaxel 20 mg/m²/week, the trial was closed to accrual. Hence, the MTD recommended for future phase II studies is thalidomide 100 mg twice daily with docetaxel 25 mg/m²/week.

Clinical benefit was seen at all cohort levels except at the highest dose level of thalidomide, despite using low weekly doses of docetaxel. Prolonged progression free intervals were observed for eight of 18 patients (44.4%) that completed cycle one. These progression free intervals ranged from 99 to 332 days. One patient, with advanced melanoma, treated at the dose level of thalidomide 100 mg twice daily and docetaxel 10 mg/m²/week enjoyed a 332 progression free interval. There did not seem to be a correlation between dose level and response.

Although anti-angiogenic agents, especially when combined with chemotherapy, result in tumor shrinkage, they more frequently stabilize disease [3]. Therefore, when using these anti-vascular therapies, overall survival and freedom from progression may be the most important clinic events, as opposed to objective tumor response. A review of phase I trials for single agent anti-angiogenic agents showed an overall response rate of 4%, complete response rate of <1%, but clinical benefit (stable disease or response not meeting partial response criteria) in one-third of patients, showing that RECIST criteria may be a suboptimal measurement [49]. This data fits with our 50% partial response and freedom from progression rate.

There are a variety of novel anti-angiogenic and anti-vascular drugs currently in clinical use. Targeting multiple or redundant steps along the angiogenesis pathway may reduce the risk of tumors developing resistance by activating alternative pathways or production of pro-angiogenic factors [2, 5, 6]. Future development of low dose metronomic schedules should be pursued with these and other novel potent anti-angiogenic agents. These combinations will hopefully offer low toxicity and delayed development of drug-resistance, along with clinical efficacy, by targeting the tumor vasculature endothelium over a prolonged time. The goal for these regimens may be tumor stabilization and freedom from progression rather than tumor regression. The long-term side effects of these regimens are to be determined.

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