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ORIGINAL ARTICLE

A phase II study of milataxel: a novel taxane analogue in previously treated patients with advanced colorectal cancer

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Abstract
Background Milataxel is a novel taxane analog, with evidence of enhanced preclinical activity compared to paclitaxel and docetaxel, especially in cell lines that over express P-glycoprotein. Based on preclinical data that milataxel may be active in colorectal cancer (CRC), a phase II study was performed in patients with advanced previously treated CRC.
Patients and results Forty-four eligible patients were entered. Milataxel was administered intravenously every 3 weeks at the dose of 35 mg/m^2. No objective responses were noted, stable disease was seen in three patients. The median time to progression was 1.4 months (95% CI of 1.2–2.4 months). Three subjects developed neutropenic sepsis and two died. The most frequent grade 3/4 adverse events were neutropenia (57%), leukopenia (27%), dehydration (14%), neuropathy (16%), diarrhea (14%) and thrombocytopenia (14%). The pharmacokinetics of milataxel was assessed in five subjects. The mean milataxel elimination half-life was 64 h and the mean area under the plasma concentration-time curve was 1,708 ng·h/ml.

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Conclusions A syndrome of neutropenic sepsis and diarrhea can be life threatening and close surveillance is needed in patients treated with milataxel at the dose of 35 mg/m^2 every 3 weeks. Clinical activity was not demonstrated in patients with advanced previously treated CRC.

Keywords Colorectal cancer · Phase II · Milataxel · MAC-321 · Taxanes

Introduction

Colorectal cancer (CRC) is a common disease worldwide, and in the United States about 146,000 new cases are expected in 2006 [1]. There have been rapid advances in the development of new chemotherapeutic drugs for CRC in the last decade. These changes have improved the outcome especially for patients with untreated advanced CRC [2]. In this group, the standard of care, at this time, is 5-fluorouracil (5-FU) combined with other drugs, such as irinotecan, oxaliplatin and bevacizumab [2–4]. However, the outcome for patients who have failed a first line, multiagent regimen are still poor. Response rates to single agent salvage chemotherapy is in the range of 4–12% and median survival times are still less than 1 year [5–9].

Milataxel [MAC-321, TL139, (microtubule/apoptosis/cytotoxic: 5beta, 20-epoxy-1, 2α-, 4-, 7β-, 10β-, 13α-hexahydroxytax-11-en-9-one 4 acetate 2 benzoate 7-propionate 13-ester with (2R,3S)-*N*-tertbutoxycarbonyl-3-(2-furyl)isoserine)] is a novel taxane analog of docetaxel. Milataxel is similar to the taxanes and enhances the rate of tubulin polymerization [10, 11]. A major advantage of milataxel is the ability to overcome P-glycoprotein mediated resistance to paclitaxel and docetaxel. Preclinical studies of milataxel in a number of cell lines including colon (HCT-116, HT29), reveled significant inhibition both with an oral and IV formulation [10]. Unlike paclitaxel and docetaxel, the IC (50) of milataxel did not vary in cells that expressed low to moderate levels of P-glycoprotein [10]. In KB-V1 cells, which highly over express P-glycoprotein, milataxel was more active compared to paclitaxel and docetaxel [10].

Resistance to paclitaxel may also be mediated by a mutation in the paclitaxel binding region of beta tubulin [11–13]. In cell lines that contain such distinct point mutations, milataxel showed similar or less resistance compared to paclitaxel and docetaxel [10].

Unlike the paclitaxel and docetaxel, milataxel does not require formulation with polysorbate 80 or cremophor, which can result in hypersensitivity reactions. Both paclitaxel and docetaxel have poor oral bioavailability, most likely due to high levels of P-glycoprotein in the gut [14]. In addition, metabolism of docetaxel by cytochrome P450 (CYP) 3A4 in gut and liver may also contribute to poor bioavailability. Milataxel, however, has shown good oral bioavailability in early trials. Based on these promising preclinical data, phase I studies were conducted both with an oral and IV formulation.

In the first human study, milataxel was administered as an IV infusion over 4 h every 3 weeks to 26 patients. The starting dose was 1.25 mg/m^2 and doses were escalated using a two-stage accelerated schema [15]. Dose limiting toxicity (DLT) was seen at the dose of 45 mg/m^2 and consisted of myalgias, dyspnea, and neutropenia. Based on this study the dose of 35 mg/m^2 every 3 weeks was chosen for subsequent phase II studies. An oral formulation of milataxel has also been evaluated. Milataxel was administered orally once every 21 days up to a dose of 60 mg/m^2, and DLT was neutropenic fever in this study [16].

Based on the excellent preclinical data showing activity in cell lines including colon cancer, and the ability to overcome the multi drug resistant (MDR) phenotype [17], we conducted a phase II study of milataxel in patients with previously treated advanced CRC. The objectives of this study were to evaluate the response rate and safety profile of milataxel in patients with advanced CRC. The pharmacokinetics (PK) of milataxel was also evaluated in a subset of patients.

Patients and methods

Patient selection

Eligible patients (>18 years old) had failed ≥1 prior approved chemotherapy regimen for metastatic disease. All patients had histologically confirmed adenocarcinoma of colon or rectum, and were required to have measurable disease. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; Adequate organ function was required [serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times the upper limit of normal (ULN), serum bilirubin ≤1.5 × ULN]. In the presence of liver metastasis AST, ALT ≤5 × ULN and serum bilirubin ≤3 × ULN was allowed. Patients were required to have serum triglycerides ≤750 mg/dl, absolute neutrophil count (ANC) >1,500cells/mm^3 and platelet >100,000 cells/mm^3. Life expectancy of ≥12 weeks was also required.

Pertinent exclusion criteria were: prior therapy with milataxel; >4 treatment regimens (including adjuvant therapy); Grade ≥2 peripheral neuropathy, radiation therapy to >25% of bone marrow; brain metastasis; known hypersensitivity to taxanes, and pregnant or nursing women. All patients signed an informed consent prior to therapy, according to institutional and federal guidelines. The study was carried out at 12 sites in the United States.

Study assessments and requirements

Prior to the start of treatment, a history and physical exam (H&P) including a detailed neurological exam, complete blood count (CBC), chemistries including liver function tests, urine analysis, ECG and radiological scans to define extent of tumor were performed. Patients were followed with weekly CBC and chemistries. Toxicity assessment was performed weekly by telephone and an H&P was done every 3 weeks. Radiological scans were performed every 6 weeks. Toxicity was graded according to the common toxicity criteria (CTC) version 2.0.

Drug therapy

Milataxel (Wyeth Research, Philadelphia, PA) was supplied as a powder in 10-ml amber vials each containing 40 mg of drug. USP anhydrous ethanol (10.5 ml) was added to reconstitute. Once dissolved, the solution was added to prelabeled EVA IV administration bag. The Liposyn (200 ml) was then transferred to the EVA administration bag. For the first dose, the drug was administered at the rate of 0.5 ml/min over 15 min. If no reaction occurred, the remaining milataxel was given over 3 h and 45 min. All subsequent infusions were given over 4 h at a constant rate. The duration of one cycle of therapy was 3 weeks. Antiemetic therapy was at the discretion of the investigator according to institutional guidelines.

Dose modifications

A maximum of two-dose reductions and a 2-week delay for drug administration in case of toxicity was were permitted. Dose reductions were done in 25% decrements. Patients were required to meet pre-study laboratory requirements prior to dosing on each subsequent cycle.

Hematologic toxicity

If platelet count was <100,000 cells/mm^3 on day of treatment or grade 4 thrombocytopenia was seen at any time, a 25% dose reduction was mandated. If ANC was <1,500 cells/mm^3 on day of treatment or grade 4 neutropenia >5 days or any grade neutropenia with fever was documented, then patients were treated with a 25% dose reduction on recovery.

Non-hematologic toxicity

If grade 2 or 3 toxicity (excluding nausea, vomiting, alopecia, or diarrhea based on investigator discretion) was seen on day of treatment, then on recovery doses were reduced by 25%. If grade 2 neurotoxicity lasted more than 5 days, then dose was also reduced by 25%. If a grade 4 toxicity occurred or for grade 3 neurotoxicity lasting more than 5 days, patients were taken off study.

Evaluation of response

Radiological tests were performed at baseline and every 6 weeks to assess the response. The RECIST criteria were used to assess response [18].

Trial design and statistics

The study used a two-stage group sequential design [19] that had 80% probability to identify as effective a drug with a response rate of 15 and 95% probability to reject as ineffective a drug with a response rate of 6%. If less than three responses were to occur in the first 31 patients enrolled, the trial would end, and the treatment would be rejected. If at least three patients responded, then 51 additional patients were to be enrolled for a total of 82. If $\leq$7 patients out of 82 responded, the drug would be declared ineffective; otherwise the agent would be declared sufficiently effective to warrant further study. An interim analyses for response was performed when 31 patients were accrued, accrual continued during this time till analysis was complete.

Pharmacokinetic analysis

Plasma samples were collected at selected clinical sites for bioanalysis and subsequent PK analysis. Blood (5 ml) samples were collected in sodium EDTA Vacutainer tubes during cycle 1, prior to infusion and at the following times points from start of infusion, 2, 4, 4.25, 4.5, 5, 6, 8, 24, 48, 72, 96, 120 and 168 h. These samples were centrifuged to separate and isolate plasma and stored at −70°C. Milataxel concentrations were determined using a validated HPLC mass spectrometry method (Xenobiotic Laboratories, Inc. Plainsboro, NJ) that utilized a typical solvent extraction technique. The mean area under the curve (AUC) of milataxel was determined using standard model independent methods. The elimination half-life ($T_{1/2}$) was estimated during the log-linear portion of the plasma concentration time profile.

Results

Patient population

Forty-five (45) subjects were enrolled in the study from March 2003 to August 2003, 44 patients were evaluable and received at least one dose of drug. A total of 188 cycles

were administered, range 1–6 cycles and median 2 cycles/patient. Patient characteristics are presented in Table 1. All patients had prior exposure to 5-flurouracil or capecitabine, and the majority had prior exposure to irinotecan and oxaliplatin. Only one patient had prior therapy with bevacizumab and no patients had prior cetuximab therapy. The majority (87%) of the patients had liver metastasis at presentation. Interim analysis for response was performed when 31 patients were accrued. Due to rapid accrual, 44 evaluable patients were entered prior to terminating the study due to inactivity.

Efficacy

For the intent-to-treat population, all 45 subjects enrolled were included in the efficacy analysis. There were no objective responses, 3 subjects had confirmed stable disease. The median time to progression was 1.4 months (95% confidence interval of 1.2–2.4 months).

Safety

Toxicities were assessed as possibly, probably or definitely related to treatment (Table 2). Safety analysis includes 44 patients who received at least one dose of milataxel. The most common adverse events (all grades) were neutropenia (66%), asthenia (62%), nausea (48%), arthralgia (43%), myalgia (43%), leukopenia (41%), neuropathy (41%), anorexia (32%), anemia (30%) and abdominal pain (18%).

Eight (8) subjects discontinued treatment due to toxicity; the most commonly reported event leading to discontinuation was neuropathy, which occurred in five subjects. Dose reductions occurred in 8 subjects after cycle 1; the most common reasons for dose reductions were neutropenia ($n = 4$) and neuropathy ($n = 3$). Dose delays occurred in 6 subjects; the most common reason for dose delays was neuropathy ($n = 4$). Six patients developed neutropenic sepsis and two died as a result. The two deaths occurred 13 and 16 days after the first dose of milataxel.

Table 1 Patient demographics

Parameter	($n = 45$)
Sex	
Male	27 (60%)
Female	18 (40%)
Age (years)	
Median	59
Range	38–80
Ethnicity	
White	33 (73%)
Other[a]	12 (27%)
Performance status (ECOG)[b]	
0	21 (48%)
1	22 (50%)
2	1 (2%)
Prior therapy	
Radiation therapy	6 (13%)
Surgery	44 (98%)
Prior chemotherapy	100%
1 Regimen	7 (16%)
2 Regimens	28 (62%)
3 Regimens	9 (20%)
4 Regimens	1 (2%)
Drug exposure	
5-FU/capecitabine	45 (100%)
Irinotecan	41 (92%)
Oxaliplatin	39 (87%)

ECOG-Eastern Cooperative Oncology group

[a] Other included African American (5), Hispanic (4), and Asian (3)

Table 2 Selected treatment related treatment-adverse events

Toxicity	(Patients, $n = 44$)	
	Grade 1/2	Grade 3/4
General		
Asthenia	24 (55%)	3 (7%)
Dehydration	3 (7%)	6 (14%)
Fever	6 (14%)	1 (2%)
Infection	3 (7%)	3 (7%)
Gastrointestinal		
Abdominal pain	7 (16%)	1 (2%)
Anorexia	13 (30%)	1 (2%)
Diarrhea	10 (23%)	6 (14%)
Nausea	18 (41%)	3 (7%)
Vomiting	8 (18%)	4 (9%)
Hematological		
Anemia	8 (18%)	5 (11%)
Leukopenia	6 (14%)	12 (27%)
Neutropenia	4 (7%)	25 (57%)
Thrombocytopenia	3 (7%)	6 (14%)
Musculoskeletal		
Arthralgia	18 (41%)	1 (2%)
Myalgia	14 (32%)	5 (11%)
Neurological		
Neuropathy	11 (25%)	7 (16%)

Pharmacokinetic results

The pharmacokinetics of milataxel was assessed in five subjects on cycle 1 (Table 3). The mean milataxel elimination half-life was 64 h and the mean AUC was 1,708 ng·h/ml following a dose of 35 mg/m^2 given over 4 h. The maximum concentrations ranged from 70 to 156 ng/ml, $T_{1/2}$ ranged from 37 to 106 h (mean of 64 h). Milataxel AUC ranged from 865 to 2,122 ng·h/ml (mean 1,708 ng·h/ml).

Table 3 Milataxel pharmacokinetic parameter in cycle 1

Dose (mg/m^2)	Statistic	C_{max} (ng/m^2)	T_{max} (h)	AUCt (ng*h/ml)	AUC (ng*h/ml)	$T_{1/2}$ (h)	CL ($L/h/m^2$)	V_{ss} (L)
35	No of patients	5	5	5	5	5	5	5
	Mean	112	3.20	1458.24	1707.77	63.87	22.8	1556.86
	SD	40.6	1.8	486	492	28.1	10.0	728.2

C_{max} maximal concentration, T_{max} time to maximal concentration, *AUC* area under the concentration versus time curve, *CL* clearance, V_{ss} volume of distribution at steady-state, AUC_t area under the concentration versus time curve to last observable concentration, *SD* standard deviation

Discussion

The primary objective of this study was to evaluate the clinical activity of milataxel in patients with advanced CRC. However objective response was not observed, and study was terminated after an interim analysis was performed. Due to termination of study, analysis of other secondary endpoints (quality of life and overall survival) were not evaluated. The median time to progression of 1.4 months is disappointing. Agents which are active in previously treated CRC include irinotecan, oxaliplatin (with 5-FU), cetuximab and panitumumab [5–9]. In general, a response rate of 10% is considered as the benchmark to evaluate single agents in the refractory setting. Despite encouraging preclinical activity, in particular efficacy in cells overexpressing P-glycoprotein, milataxel was not active in CRC. The mechanism of taxane resistance, especially for second-generation taxanes in colon cancer remains unclear. It may be that preclinical and xenograft models are poor predictors of clinical activity in colon cancer [20, 21]. The PK profile of milataxel in this study is similar to data previously published [15, 16].

Milataxel administration resulted in neutropenic sepsis in 6 (14%) patients, and two deaths. A small number of subjects treated with milataxel among several studies have developed a fulminant syndrome within 1–2 weeks after initial exposure. The syndrome was characterized by severe neutropenia and diarrhea, resulting in sepsis, primarily with bowel and gastrointestinal organisms. Subjects at risk for this syndrome may include those with elevated serum alkaline phosphatase and/or total bilirubin. This syndrome was also associated with a rapid rise in serum bilirubin levels typically detected 1 to 2 weeks following initial treatment. Three (3) subjects in this study, including the two fatalities, may have been among the subjects manifesting this syndrome. Data for all relevant subjects in milataxel clinical trials have been reviewed by an independent expert panel, which recommended continued clinical evaluation of milataxel with appropriate monitoring. In this study hemopoietic growth factors were allowed if clinically indicated after two cycles of milataxel. Based on the degree of neutropenia and neutropenic fever, prophylactic hemopoietic growth factor support would be beneficial if a dose of 35 mg/m^2 of milataxel is used in future studies. The PK profile in patients with altered liver function also needs to be determined. The other adverse events seen in this study of neuropathy and myalgias are common to the taxanes. Hypersensitivity reactions were not observed with milataxel administration.

In summary milataxel is inactive in patients with previously treated advanced CRC. However, a phase II study in non-small cell lung cancer was conducted with four objective responses (one complete and three partial responses) in 32 evaluable patients for a 13% response rate. In this study, where milataxel was administered at the dose of 35 mg/m^2 every 3 weeks, responses were seen in patients who had previously been treated with platinum based chemotherapy regimens, as well as prior taxane therapy [22]. In addition, in a phase I weekly dosing study, there were two objective responses in ten evaluable breast cancer patients for a response rate of 20% [23]. Based on these observations, milataxel may be worth further evaluation in taxane sensitive diseases such as breast, lung and ovarian cancers. Furthermore, continued research is necessary to develop new agents and to understand the mechanisms of the MDR phenotype in CRC.

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