Multicenter Phase II Trial of Motexafin Gadolinium and Pemetrexed for Second-Line Treatment in Patients with Non-small Cell Lung Cancer

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Background: Motexafin gadolinium (MGd) disrupts redox-dependent pathways by inhibiting oxidative stress-related proteins leading to apoptosis. MGd selectively targets tumor cells, disrupting energy metabolism and repair mechanisms, rendering cells more prone to apoptosis. Preclinical studies with MGd and pemetrexed show significant tumor growth delay in lung cancer cell lines.

Methods: Patients with non-small cell lung cancer, Eastern Cooperative Oncology Group performance status 0 to 1, who had received one previous platinum containing regimen and normal organ function were treated with MGd 15 mg/kg and pemetrexed 500 mg/m^2 q21days. Patients were allowed to receive more than one regimen if the initial treatment was in the adjuvant or curative setting and administered >12 months earlier. The primary end point was to demonstrate a 40% rate of 6-month progression free survival (PFS).

Results: Seventy-two patients (30 women, 42 men), performance status 0/1 (30/42), and a median age of 63 years were enrolled. Most patients (96%) were current or former smokers. All histologic types were represented (squamous/adenocarcinoma/other: 28%, 42%, 31%). Number of prior regimens: 1: 69%; 2: 26%, and >2: 4%. Median number of cycles administered was (range) 2 (1–12). Toxicity: grade 3/4 neutropenia was noted in 8.3% with febrile neutropenia in 1.4%, thrombocytopenia in 8.3%, fatigue in 9.7%, and pneumonia in 11.1%. There were no complete responses, 8.1% had partial response, 56.5% had stable disease, and 35.5% had progressive disease as their best response. Twenty-three percent of patients were progression free at 6 months and the median PFS was 2.6 months with an overall survival of 8.1 months.

Conclusions: The combination of MGd and pemetrexed was well tolerated with toxicity similar to that of pemetrexed alone. However, the study did not achieve its end point of 40% 6-month PFS. The response rate, PFS, and overall survival did not seem markedly different than prior phase II and phase III studies of pemetrexed alone. Consequently, there are no further plans for development of this combination.

Key Words: Lung cancer, Motexafin gadolinium, Pemetrexed, Second line.

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Three agents are currently approved for second-line therapy for non-small cell lung cancer (NSCLC) after initial treatment with platinum-based combinations: docetaxel, pemetrexed, and erlotinib. In a randomized trial, docetaxel was improved survival compared with best supportive care and was also demonstrated to be superior to other chemotherapy regimens (vinorelbine or ifosfamide) in terms of response and landmark survival.[1,2] Pemetrexed was shown to be as effective as docetaxel in a randomized trial, with a response rate of 9.1% compared with docetaxel of 8.8%.[3] Both agents had a median progression-free survival (PFS) of 2.9 months. Because of a lower incidence of most toxicities, particularly neutropenic fever and hospital admissions, pemetrexed is now commonly used for second-line chemotherapy.

The investigational agent, motexafin gadolinium (MGd), disrupts redox-dependent pathways by inhibiting oxidative stress-related proteins leading to apoptosis.[4] MGd selectively targets tumor cells, disrupting energy metabolism and repair mechanisms, rendering cells more prone to apoptosis with or without the addition of radiation and chemotherapy.[5] Preclinical studies with MGd and radiation or a wide range of chemotherapy agents including pemetrexed, demonstrated significant tumor growth delay in lung cancer cell lines, suggesting potential synergy between the two drugs.[6–10] Evidence from phase III trials suggests that there is clinical benefit from the addition of MGd in addition to radiation therapy in patients with metastatic NSCLC.[11–13] Given the preclinical studies and evidence from clinical trials of the potential efficacy of MGd in NSCLC and synergy with pemetrexed, we designed this pilot phase II open-label trial to

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test the hypothesis that this combination would be both well tolerated and improve outcome in the second line therapy for NSCLC.

PATIENTS AND METHODS

Patient Population

To be eligible to participate in this study, a patient should have been ≥18 years old and have a histologically or cytologically confirmed diagnosis of stage IIIb/IV NSCLC. Additionally, patients should have received one prior platinum-based chemotherapy regimen, have measurable disease per RECIST, an Eastern Cooperative Oncology Group performance status score of 0 or 1, no evidence of end-organ dysfunction, and be willing and able to provide written informed consent. Symptomatic or uncontrolled (untreated or treated and progressing) brain metastases or evidence of meningeal metastasis were also excluded. Patients were allowed only one prior palliative cytotoxic regimen (not counting adjuvant or neo-adjuvant cytotoxic chemotherapy if completed >12 months before the palliative regimen). Any prior chemotherapy, radiation therapy, experimental therapy, immunotherapy, or systemic biologic anticancer therapy should have ended at least 21 days before beginning study treatment, and all toxicities related to the previous treatment must have resolved or stabilized. Additional exclusionary criteria included a known history of porphyria, glucose-6-phosphate dehydrogenase deficiency, or HIV seropositivity, though testing for these conditions was not required at the screening visit, as well as any comorbidity, which interferes with the ability to tolerate the protocol therapy assessments.

Treatment

MGd 15 mg/kg was administered once during the first week of each 3-week cycle by intravenous infusion over 60 minutes and given before pemetrexed 500 mg/m^2 IV infused over 10 minutes. A maximum of 12 cycles of treatment was permitted on this protocol. All patients received folic acid ≥400 μg/d starting 7 days before first study treatment and continuing through 21 days after last study treatment; vitamin B_{12} 1 mg within 7 days before first study treatment and on day 1 of cycles 4 and 8; and dexamethasone 4 mg bid the day before, day of, and day after each study treatment. Antiemetics were given at the discretion of each investigator.

Objectives and Statistical Plan

The primary end point was 6-month PFS defined as the time from first dose of MGd to the earlier of progression or death. Patients who were still alive and who had not progressed by the time of their last response assessment were censored at that time. PFS was plotted using the Kaplan-Meier method. For the purposes of the sample size calculation, and based on the previous studies of docetaxel and pemetrexed as single agents in this setting, a null PFS rate of 25% was assumed for 6-month PFS. An evaluable sample size of 62 provided 80% power to reject the null hypothesis of PFS of 25% when the true PFS rate is 40%. These calculations were performed using the exact binomial test with a two-sided alpha rate of 0.10.

Secondary objectives were time to progression, defined as the time from the first dose of MGd to the first evidence of progression, and overall survival. The patient population for this end point consisted of all patients who received at least 1 dose of MGd and pemetrexed and underwent at least 1 response assessment. Patients who had not progressed by the time of their last response assessment were censored at that time. Time to progression and overall survival were determined using the Kaplan-Meier method.

Response, duration of response, and clinical benefit ratio (complete response + partial response + stable disease) were all determined using the RECIST.[14] Toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 3.0. The study was approved by the institutional review board of each participating institution before patient enrollment at that institution. All patients provided written informed consent. The study was registered with clinicaltrials.gov (NCT00365183).

RESULTS

The study opened on July 12, 2006, and completed enrollment on August 26, 2008. A total of 72 patients enrolled and received at least one dose of therapy. Sixty-two patients are evaluable for response. The demographics of the study population are in Table 1. Of note, virtually all the patients had significant history of tobacco use. Twenty-eight percent had squamous cell carcinoma as this trial was completed before the observation that pemetrexed is preferentially effective in adenocarcinoma.[15] An exploratory analysis did not demonstrate any benefits for that subset (median survival for squamous versus nonsquamous, 244 versus 284 days, respectively). The combination was well tolerated with an overall level of toxicity similar to that seen with pemetrexed as a single agent (Table 2). There were two grade 5 toxicities. In both patients, neutropenia and sepsis developed after treatment. One patient, a 70-year-old man, developed neutropenia and sepsis after the first course of therapy and

TABLE 1. Patient Demographics

Characteristic	*N*
Age, median (range)	63 yr (37 – 83 yr)
Sex (M/F)	42/30
ECOG PS 0/1	30/42
Race	
African American	6
White	66
Histology	
Squamous/nonsquamous	20/52
Response to first-line therapy	
No response	13
Response, TTP <3 mo	26
Response, TTP >3 mo	33

ECOG PS, Eastern Cooperative Oncology Group performance status; TTP, time to progression.

TABLE 2. Major Toxicities

	Grade		
Toxicity	**3**	**4**	**5**
Hematologic			
Hemoglobin	8	0	0
Neutropenia	1	5	0
Thrombocytopenia	1	5	0
Febrile neutropenia	1	0	0
Nonhematologic			
Gastrointestinal	7	0	0
Cardiac	3	1	0
Fatigue	6	1	0
Infection	9	0	2

TABLE 3. Response and Survival

Characteristic	***N***
Response	
Assessable	62
Not assessed	10
Best overall response	
CR	0
PR	5
SD	35
PD	22
6-mo PFS (%)	23%
Progression-free survival, d	78
Median overall survival, d	244
1-yr survival (%)	36%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival.

subsequently developed bowel obstruction, gastrointestinal hemorrhage, and aspiration pneumonia leading to death. The other patient, a 63-year-old woman, experienced neutropenic sepsis and pneumonia after nine courses of pemetrexed and motexafin and ultimately died of cardiogenic shock. Unfortunately, the 6-month progression free survival, overall survival, response rate, clinical benefit ratio were also similar to that which would be expected from pemetrexed as a single agent (Table 3).

DISCUSSION

MGd is a tumor selective anticancer agent with a novel mechanism of action. It has a strong affinity for electrons, meaning that it is easily reduced.[4] MGd accepts electrons from various intracellular metabolites and enzymes, such as ascorbate, NADPH, glutathione, and thioredoxin reductase in the presence of oxygen, MGd transfers the electrons to oxygen to produce reactive oxygen species, such as superoxide and hydrogen peroxide, and regenerates the MGd molecule by a process referred to as "futile redox cycling."[16] MGd is also able to oxidize protein thiols, which may alter protein structure. As a result of these effects, MGd disrupts cellular metabolism within the cancer cell, inhibiting DNA repair and promoting apoptosis. In addition, MGd directly inhibits the activity of thioredoxin reductase.[5]

MGd selectively accumulates in cancer cells, which has been confirmed in vivo and in patients using magnetic resonance imaging scanning to detect the biodistribution of the paramagnetic, Gd (III)-containing complex.[17] It is possible that the tumor selectivity demonstrated by MGd is a consequence of the altered redox state of these tissues or other factors present in the tumor microenvironment, such as the elevated rates of anaerobic glycolysis, a lowered tissue pH, nutrient supply limitations, and hypoxia.

In preclinical models, MGd has been shown to be cytotoxic to some lung cancer cell lines in vitro, both as a single agent and in combination with various chemotherapy drugs and radiation therapy. In A549 human lung cancer cells cultured in vitro, MGd is cytotoxic after 12 hours incubation at 50 μM, a concentration achievable in humans. Because of its multifunctional mechanism, cancer cells exposed to MGd may be more vulnerable to many types of oxidative stress including that caused by radiation therapy and chemotherapy.[7,18] As noted above, MGd has been shown to enhance the in vitro and in vivo effects of a variety of chemotherapeutic agents. The combination of MGd and pemetrexed was studied in lung cancer cell lines both in tissue culture and in an animal xenograft model and demonstrated synergy.[6]

The primary focus of MGd clinical development has been as a tumor selective radiation enhancement agent.[19,20] In a randomized phase III trial of brain metastases (PCYC-9801), a subset analysis demonstrated improved response, prolonged time to neurologic and neurocognitive progression and function in patients with brain metastases secondary to NSCLC.[12] Unfortunately, a phase III confirmatory international study (PCYC-0211) confined to NSCLC brain metastases failed to meet its predefined end point of prolonged time to neurologic progression. However, in the intent-to-treat analysis, MGd exhibited a favorable trend in neurologic outcomes. MGd significantly prolonged the interval to neurologic progression in NSCLC cancer patients with brain metastases receiving prompt whole brain radiation therapy and reduced the need for salvage brain surgery. The overall negative result appeared to be attributable to an unexpected influence of treatment delays in radiation therapy.[13]

MGd has been studied extensively in patients with lung cancer. In a single dose phase I trial, the selective localization of MGd in primary lung cancer, hilar lymph nodes, and other metastatic sites was confirmed using magnetic resonance imaging.[19]A phase II trial has evaluated MGd as a single agent in progressive NSCLC with evidence of activity in the form of disease stabilization.[21] The experience combining MGd with chemotherapy is much more limited. One prior phase I trial combined the agent with docetaxel in advanced solid tumors.[22] A phase I trial restricted to NSCLC with docetaxel and cisplatin and MGd demonstrated tolerability, but there was no significant improvement of activity.[23] Given its excellent tolerability, tumor selectivity and preclinical synergy with pemetrexed, evaluation in combination with pemetrexed was a logical approach. However, despite the ample preclinical data and previous observations demonstrat-

ing single agent activity for MGd, there was no evidence of benefit for this combination. It is possible that alternative dosing schedules or combinations of other agents with MgD could demonstrate some level of clinical benefit.

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