Phase II Study of Temozolomide for Relapsed Sensitive or Refractory Small Cell Lung Cancer

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ABSTRACT

Background: Temozolomide is an alkylating agent approved for use in patients with glioblastoma multiforme and refractory astrocytoma. We designed this phase II study of temozolomide in patients with SCLC based on the following rationale: alkylating agents have established efficacy in SCLC; temozolomide penetrates into the central nervous system with the potential to treat the brain metastases commonly seen in SCLC; SCLC has aberrantly methylated *MGMT*, which is correlated with improved outcomes to temozolomide in glioma; anecdotal responses to temozolomide in patients with SCLC have been observed.
Methods: Temozolomide is administered to patients with relapsed sensitive (relapse after 60 days) or refractory (no response to initial therapy, or progression within 60 days) SCLC. Patients who have disease progression after 1 or 2 prior chemotherapy regimens are eligible. Additional eligibility criteria include Karnofsky performance status ≥ 60% and normal organ and marrow function. The primary endpoint is objective response rate. Temozolomide is administered daily for 21 consecutive days of a 28-day cycle. The starting dose for the first cycle is 75mg/m^2/day. For those patients without grade 3 or higher toxicities at that dose, in subsequent cycles a single dose escalation to 100mg/m^2/day is given. Treatment is to be continued until documentation of disease progression, unacceptable toxicity or withdrawal. The target accrual is 64 patients. *MGMT* promotor methylation status is assessed in available tissue and in peripheral blood.
Results: Twenty-five patients (12 men, 13 women) have been accrued to date, of which 16 patients have sensitive and 9 have refractory SCLC. Temozolomide was second- and third-line treatment for 13 and 12 patients, respectively. Thirteen patients have brain metastases. The median age is 66 (range 49 to 79). Twenty-three patients are assessable for response. Three patients have achieved a partial response and six patients have stable disease. The remainder of the patients have had progression of disease within one cycle of treatment. Four patients have received two cycles and three patients have been treated beyond two cycles of temozolomide. The overall response rate is 13%. Regressions have been observed in five patients with progressive brain metastases, including two patients with recurrent disease after prophylactic cranial irradiation and whole brain radiation therapy. Toxicities include: grade 3 lymphopenia (20%; requiring initiation of pneumocystis prophylaxis); grade 3 thrombocytopenia (4%); grade 1/2 fatigue (32%); grade 1/2 emesis (20%); and grade 3 rash/pruritus (8% each).
Conclusions: 1) In this ongoing trial, three partial responses have been seen in patients with sensitive SCLC. 2) Temozolomide causes regression in SCLC brain metastases. 3) Temozolomide is well tolerated when given on this dose and schedule. 4) At this time, seven samples analyzed for *MGMT* hypermethylation have not demonstrated methylation.

BACKGROUND

- Topotecan is the only FDA-approved agent for the second-line treatment of SCLC.
- There are no accepted regimens for patients who have failed first- and second-line treatments for SCLC.
- The *MGMT* (O^6 methyl-guanine-DNA methyltransferase) gene encodes the DNA-repair protein O^6 alkyl-guanine (O^6-AG) DNA alkyltransferase.
- This protein removes alkyl groups from O^6 position of guanine, an important site of DNA alkylation. (Gerson SL. *J Clin Oncol* 2002)
- Aberrantly methylated *MGMT* is found in SCLC. (Esteller M, et al. *Oncogene* 2004)
- Epigenetic silencing of the *MGMT* gene via hypermethylation of specific CpG islands is associated with:
- Increased carcinogenic risk.
- Improved sensitivity to alkylating agents. (Esteller M, et al. *Oncogene* 2004)
- Temozolomide is a nonclassic oral alkylating agent.
  - Good penetration into the CNS as it crosses the blood brain barrier.
  - Approved for use in patients with newly diagnosed glioblastoma multiforme and refractory astrocytoma.
    - Methylation of the *MGMT* gene in tumors is associated with improved outcomes in patient with glioblastoma multiforme. (Hegi M, et al. *NEJM* 2005)
  - Several phase II trials have been reported using temozolomide in patients with brain metastases from solid tumors, including SCLC. (Abrey LE, et al. *J Neurooncol* 2001; Antonadou D, et al. *J Clin Oncol* 2002; Christodoulou C, et al. *Ann Oncol* 2001)

OBJECTIVES

- To determine the objective response rate (PR + CR) to temozolomide as a second or third line treatment in two independent cohorts of patients with advanced SCLC, those with sensitive disease and those with refractory disease.
  - **Sensitive disease:** Relapse 60 days, or 2 months, after the completion of first-line chemotherapy.
  - **Refractory disease:** No response to initial therapy, or progression within 60 days, or 2 months, after completing treatment.
- To evaluate available tumor samples for methylated *MGMT* promotor by PCR and determine if this correlates with response and survival.

METHODS

Eligibility Criteria:
- Performance status ≥ 60%; normal organ and marrow function.
- 1 or 2 prior chemotherapeutic regimens.
- Asymptomatic brain metastases (without leptomeningeal involvement).
- Measurable disease, including brain metastases.
- No chemotherapy or radiation within last 3 weeks.
- Ability to understand and sign an informed consent document.

Schema:
- Temozolomide is given daily for 21 days of a 28-day cycle.
- The starting dose for the first cycle is 75mg/m^2/day.
- For those patients without grade 3 toxicities at that dose level, a single dose escalation to 100mg/m^2/day is given in subsequent cycles.
  - Temozolomide administered until documentation of disease progression, unacceptable toxicity or patient withdrawal.
- To assess response:
  - CT scan of the chest or other clinically relevant sites during week 4 of cycles one and two, and every 8 weeks thereafter.

Design:
- Sensitive disease: Minimax Simon two-stage design
  - 23 patients will enter in stage 1
    - If ≤ 3 responses, the study will be terminated early
    - If > 4 responses, enrollment will be extended to 48
  - 12 responses out of 48 will be needed
  - This yields 80% power to detect the difference at a 5% type I error rate.
- Refractory disease: Single-stage binomial design
  - 16 patients; 2 responders will be needed
  - This yields 80% power to detect the difference at a 5% type I error rate.

***MGMT* Methylation Analysis:**
- DNA extracted and modified using standard methods.
- Methylation specific PCR used to determine methylation status of *MGMT* promoter.
- Primers designed using MSPprimer. [http://www.mspprimer.org] (Herman JG, et al. *PNAS* 1996) (Brandes JC, et al. Oncogene 2007)

RESULTS

- 25 patients have been treated with temozolomide; characteristics of the patients are listed in **Table 1**.
- 48% of the patients are men; median age of the patients is 66.
- 64% of patients had sensitive disease to etoposide/platinum doublet.
- 48% of the patients had received two lines of prior treatment.

Table 1. Patient Characteristics

Characteristic	No. of Patients (N = 25)
Gender	
Male	12
Female	13
Median Age, years	66 (Range 49-79)
Karnofsky Performance Status	
60%	2
70%	5
80%	15
90%	3
Stage at Initial Diagnosis	
Limited	5
Extensive	20
Response to First-Line Chemotherapy	
Sensitive	16
Refractory	9
Previous Lines of Treatment	
One†	13
Two‡	12
Brain Metastases	
No	12
Yes	13
New, asymptomatic	4
New, post-WBRT§	5
Treated, persistent¶	4

†All received etoposide/platinum doublet.
‡Second-line treatment included: etoposide/platinum doublet (N = 3); irinotecan/platinum doublet (N = 1); topotecan (N = 6); topotecan/obatoclax (N = 1); docetaxel (N = 1). §Post-WBRT, includes those that had prophylactic cranial irradiation, PCI (N = 3).

Table 2. Toxicities

Toxicity	No of Patients (N = 25) Grade 1	Grade 2	Grade 3
Hematologic			
Anemia	4	2	
Leukopenia	5		
Lymphopenia			5
Thrombocytopenia	4	1	1
Anorexia	1		
Fatigue	4	4	
Mucositis		1	
Nausea	1	3	
Vomiting	4	1	
Diarrhea	3	1	
Constipation	3	2	
Elevated Creatinine	1		
Dry Skin		1	
Pruritus			2
Rash/Desquamation			2

Table 3. Response to Temozolomide

	Best Response§ PR	SD	POD
Sensitive Disease (N=14)	3 (13%)†	3 (13%)‡	8 (35%)
Refractory Disease (N=9)		3 (13%)¶	6 (24%)

§Twenty-three patients are evaluable for response. †One has been confirmed with repeat imaging, two remain on study. ‡One patient removed for clinical deterioration after one cycle. ¶One patient removed for clinical deterioration after one cycle. Of the other two patients, one received 3 cycles and the other 4cycles. Abbreviations: PR, Partial Response; SD, Stable Disease; POD, Progression of Disease.

Table 4. Response in Brain with Temozolomide

	Response Decrease	Increase	Stable
Target Lesions (N=5)	1†	2†‡	2 ¶
Non-Target Lesions (N=8)§	4*	1†	2‡*

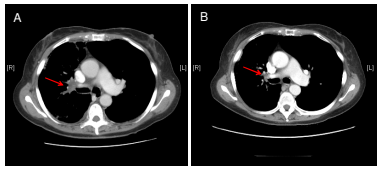
†One patient without follow-up imaging. ‡Previous PCI, new metastases. ‡Previous WBRT, new metastases. ¶Previous WBRT, existing lesions. * No previous WBRT or PCI, 3 patients with decrease size in lesions, 1 patient with stable lesions.

- The median number of cycles administered are one (range 1 week to 5 cycles).
- One patient removed from study after 1 week due to progression in brain.
- Seven patients have received ≥ 2 cycles.
- Treatment is well-tolerated and no grade 4 toxicities have been observed, **Table 2**.
  - Grade 2 and 3 thrombocytopenia have led to treatment delays.
  - Grade 3 lymphopenia has required the initiation of pneumocystis prophylaxis.

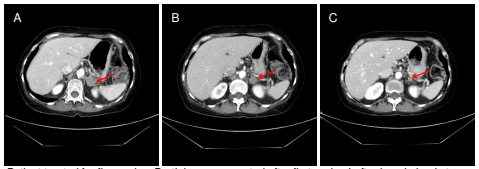
- **Three patients (13%)** have had **partial response** (one of these is confirmed), **Table 3**.
- One of these patients has had response in a target lesion in the brain.
- All of these patients had **sensitive disease** to first-line treatment.

- **Six patients (26%)** have had **stable disease**, **Table 3**.
- Two removed from study secondary to clinical deterioration after only one cycle.
- Four patients have received ≥ 2 cycles.
- Three patients each with **sensitive and refractory disease** to first-line treatment.

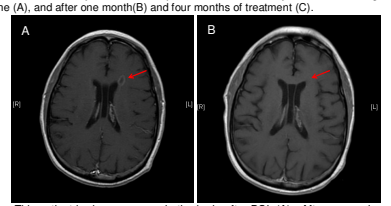
- Seven biopsy samples available for *MGMT* methylation analysis
  - All unmethylated *MGMT* gene [95% Confidence Interval, 0.0 to 0.41]
  - Best response: 1 partial response, 2 stable disease, 4 progression of disease



Patient treated for three cycles. Best response has been stable disease. Marked response in right hilar mass seen after first cycle and maintained after three cycles. (A) Baseline. (B) After three cycles.



Patient treated for five cycles. Partial response noted after first cycle. Left adrenal gland at baseline (A), and after one month(B) and four months of treatment (C).



This patient had a recurrence in the brain after PCI. (A). After one cycle of temozolomide the lesion in the left frontal lobe adjacent to the left frontal horn almost completely resolved with marked interval improvement in the remainder of the lesions (B). We are awaiting confirmatory imaging. An additional four patients have been noted to have a decrease in brain lesions after treatment with temozolomide, including one patient who had received whole brain radiation therapy, see **Table 4**.

CONCLUSIONS

- Three partial responses have been seen in patients with sensitive SCLC.
- In patients with refractory SCLC, no responses have been noted; just stable disease.
- Temozolomide causes regression in SCLC brain metastases.
- Treatment with temozolomide is well-tolerated.
- *MGMT* promotor hypermethylation has not been observed in tissue samples.
- Additional tumor samples are available and this evaluation is ongoing.

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