ANG1005: PRELIMINARY CLINICAL SAFETY AND TOLERABILITY IN PATIENTS WITH RECURRENT MALIGNANT GLIOMA

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ABSTRACT

Background: The blood–brain barrier (BBB) complicates the clinical treatment of most CNS diseases, including malignant glioma (MG). Angiopep-2 is a 19 amino acid peptide shown in animal models to cross the BBB using a physiological approach through transcytosis by binding to low-density lipoprotein receptor-related protein (LRP) expressed on the surface of the BBB. ANG1005 is a new chemical entity (NCE) that combines 1 molecule of Angiopep-2 with 3 molecules of paclitaxel. Preclinical studies demonstrate the brain's uptake of ANG1005 to be ~100x greater than paclitaxel and ~10x greater than temozolomide. Because LRP is upregulated on MG cells, once in the brain compartment, ANG1005 uses the same receptor-mediated mechanism described above to enter tumour cells where cleavage of ANG1005 occurs, releasing paclitaxel to perform its antimitotic functions. A Phase I clinical trial was initiated in October 2007 to explore the maximum tolerated dose (MTD) and obtain data on safety, tolerability and preliminary evidence of efficacy of ANG1005 in patients with recurrent MG. **Material and methods:** A multicenter, open-label, dose escalation study of ANG1005 is being conducted in the United States with sequential dose cohorts ranging from 30-558 mg/m^2. ANG1005 is administered IV every 21 days. Study participants include adult patients with measurable disease and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 who are ineligible for standard treatment options. **Results:** As of 06-Oct-2008, 14 patients with recurrent MG have received ANG1005 (8 patients with glioblastoma multiforme, 1 with anaplastic astrocytoma, and 5 with anaplastic oligodendroglioma). No patient has discontinued from the study due to study drug-related adverse events. Dose escalation is ongoing; the anticipated next cohort is 200 mg/m^2. **Conclusion:** To date, treatment options for patients with recurrent MG are limited and prognosis is bleak because of the brain's highly evolved physiological structure. Angiopep conjugates may provide a potentially safe and effective way to treat this and other currently unmanageable CNS diseases. ANG1005 is the first of a list of compounds to be tested in this regard.

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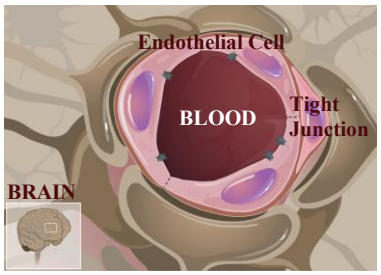
INTRODUCTION

The blood-brain barrier (BBB) is a membranic structure that constrains the passage of the overwhelming majority of small molecules, proteins and peptides between the bloodstream and neural tissue providing a natural defence against circulating toxic or infectious agents.



Physical Barrier:

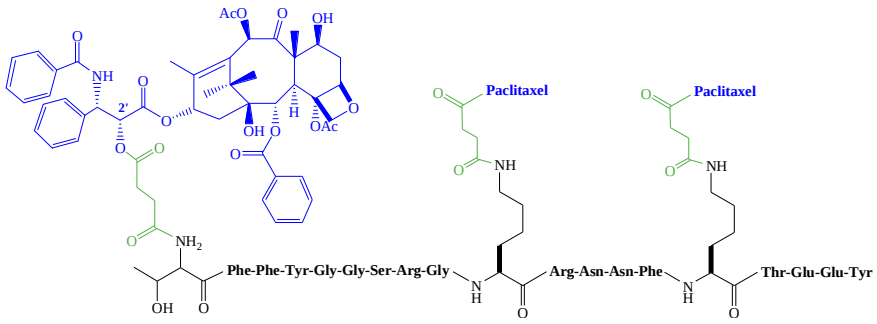
- Tight junctions between capillary endothelial cells

Physiological Barriers:

- Few alternate transport pathways
- High levels of active efflux transport proteins

Because of the BBB more than 95% of drugs cannot reach the brain, making brain diseases such as brain cancers difficult to treat. The observation that most molecules that reach the brain must interact with specific receptors that facilitate active transport across BBB endothelial cells inspired the technology discussed herein.

Angiopep-2, a 19-amino acid peptide, was designed to target the low-density lipoprotein receptor-related protein (LRP), one of a family of receptors expressed at the BBB and upregulated on the surfaces of cell lines from primary brain tumours. This vector technology is based on chemically attaching different molecules to Angiopep-2 in order to access the brain via transcytosis. ANG1005 is a NCE combining Angiopep-2 with 3 molecules of paclitaxel using cleavable ester bonds.



ANG1005 (MW=5107) : Angiopep-2 (black) conjugated with 3 paclitaxel molecules (blue); succinyl linkers (green)

Paclitaxel and other chemotherapeutics have limited use in brain cancers due to their inability to penetrate the BBB in sufficient quantities. Preclinical studies show that brain uptake of ANG1005 is ~100x greater than paclitaxel and that once in the brain compartment, ANG1005 favorably targets tumour cells which it enters by endocytosis using the same receptor mechanism. Inside tumour cells, the ester linkages that bind paclitaxel to Angiopep-2 are cleaved by esterase, found in high concentration in the lysosomes of the cells. Furthermore, the therapeutic properties of paclitaxel have been shown to be recovered once it dissociates from Angiopep-2.

Because of strong preclinical data, ANG1005 entered the clinical phase of development late last year. The present Phase I dose-finding study represents the first time ANG1005 is being administered to patients with recurrent malignant gliomas, the most common and aggressive primary brain cancers that currently have very poor prognoses.

MATERIALS and METHODS

Patients with recurrent or progressive malignant glioma (MG) are being recruited into this ongoing, sequential cohort, open-label, dose escalation study from 5 sites located in the United States (listed alphabetically).

Institution Name	Location	Principle Investigator	Study Coordinator
Cancer Therapy and Research Center	San Antonio, Texas	John Sarantopoulos, MD	Cynthia Allison, RN
Columbia University Medical Center	New York, New York	Steven Rosenfeld, MD	Mahogany Ayele, RN
Dana Farber Cancer Institute	Boston, Massachusetts	Jan Drappatz, MD	M. Brenna McNamara, RN
Henry Ford Health System	Detroit, Michigan	Tom Mikkelsen, MD	Amy Williamson, RN
MD Anderson Cancer Center	Houston, Texas	Morris Groves, MD	Kathy Hunter, RN

Objectives :

Primary:

- To characterize the safety and tolerability of IV administered ANG1005 in patients with recurrent MG
- To identify the maximum tolerated dose (MTD) of ANG1005 in patients with recurrent MG

Secondary:

- To examine the pharmacokinetics (PK) of ANG1005
- To confirm the safety and tolerability of ANG1005 at the MTD
- To assess the immunogenicity of ANG1005
- To obtain preliminary information about the antitumour activity of ANG1005 in patients with recurrent MG

Eligibility :

The study includes stable adult patients with:

- WHO grades III & IV MG which progressed following resection, first-line treatment or current standard of care;
- Measurable disease according to Macdonald response criteria;
- ECOG performance status score ≤ 2;
- Expected survival of at least 3 months;
- Haemoglobin > 9.0 g/dL, ANC > 1.5 x 10^9/L, platelet count > 100 x 10^9/L; and
- Total bilirubin < 1.5 x ULRR, AST or ALT < 2.5 x ULRR, serum calcium < ULRR, estimated Cr. Cl. > 60 mL/min.

Treatment and Evaluations :

ANG1005 is currently administered as an IV infusion at a concentration of 1.5 mg/mL and a set rate of 8.0-8.5 mL/min, ***without premedication***. Treatment is given once q 3 wks until progression, general medical deterioration that warrants discontinuation of treatment or withdrawal of consent.

Patients are closely monitored during the infusion and for up to 24 hrs after the end of infusion with weekly safety visits between treatments. AEs are collected from the time of the start of the first infusion until 3 wks after the last infusion. The severity of events is assessed according to the NCI CTCAE, v. 3.0, when possible; per protocol otherwise.

Potential neurocognitive changes are being explored through the use of a brief, simple and standardized battery of cognitive performance tests administered before, every 6 wks during, and following treatment.

Blood sampling is being done to look at the PK profile and immunogenicity of ANG1005.

In order to measure disease status, magnetic resonance imaging (MRI) is being performed at 6-wk intervals during therapy. Response is assessed using WHO response evaluation criteria modified to include consideration of corticosteroid dose.

Dose Escalation Scheme :

30 mg/m²

- Starting dose
- 1-2 pts until an emergent ANG1005-related ≥ Grade 2 toxicity (except alopecia) warrants expansion to 3 pts
- If 1 pt experiences an emergent ANG1005-related DLT, cohort is expanded to 6 pts
- Escalation will continue as long as <2 pts experience a treatment emergent DLT during cycle 1

50 mg/m²

- Modified Fibonacci Scheme - Increase of 67%

75 mg/m²

- Modified Fibonacci Scheme - Increase of 50%

105 mg/m²

- Modified Fibonacci Scheme - Increase of 40%

MTD = dose level at which ≤ 1 of 6 patients develops an emergent ANG1005-related DLT

Dose Limiting Toxicity (DLT):

- Any Grade 3 or 4 nonhematologic toxicity
- Febrile neutropenia
- Grade 4 neutropenia of ≥ 7 d duration
- Any Grade 4 thrombocytopenia
- Grade 2 peripheral neuropathy > 7 d *OR* a ≥ Grade 3 peripheral neuropathy of any duration

RESULTS

Results presented here include data up to and including October 6, 2008. 14 patients with recurrent malignant glioma (8 with glioblastoma multiforme, 1 with anaplastic astrocytoma, 5 with anaplastic oligodendroglioma) have received ANG1005 at doses ranging from 30 to 105 mg/m^2.

Patient characteristics at study entry (n = 14)

Age (years)	Median	Range	
	52	26-64	
Sex	Male	Female	
	8 (57%)	6 (43%)	
# Prior Chemotherapies	≤ 2	3	> 3
	5	3	6
Prior Radiotherapy	Yes	No	
	14	0	
ECOG at Entry	0	1	2
	8 (57%)	6 (43%)	0

Safety Data :

Safety data are available for all 14 study patients dosed to date.

No patient has discontinued from the study due to study drug-related AEs.

Preliminary neurocognitive data show that ANG1005 does not affect cognitive performance at these doses in this population. Furthermore, immunogenicity data to date indicate that ANG1005 does not elicit an immune response.

Summary of common chemotherapeutic adverse events reported by dose level and CTCAE grade

Dose Level :	30 mg/m^2			50 mg/m^2			75 mg/m^2			105 mg/m^2		
# Patients :	3 pts			6 pts			3 pts			3 pts		
Total # Cycles/Cohort :	7 cycles			10 cycles			7 cycles			2 cycles		
CTCAE Grade :	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**
Leucopenia	0	0	0	0	0	0	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0
Anaemia	0	0	0	0	0	0	0	0	0	0	0	0
Acute Infusion Reaction	1	0	0	0	0	0	1	0	0	0	0	0
Peripheral Neuropathy[1]	0	0	0	0	0	0	0	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0
Myalgia / Arthralgia[1]	0	0	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0

n = number of patients

[1] Parameter not included in CTCAE; severity assessed *per protocol*: Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening

Tumour Response Data :

6-wk tumour response data is available for 10 pts. Although efficacy is not expected at the low doses used thus far, at 6 wks, a minor response (~10% decrease) was noted in 1 GBM pt dosed at 30 mg/m^2 and stable disease was noted in 1 GBM pt dosed at 75 mg/m^2.

CONCLUSION

- **Several drug candidates exist that may treat the many currently untreatable brain conditions including brain cancers, Alzheimer's disease, multiple sclerosis, etc. Due to their large size, these therapies, mostly biologic, cannot cross the blood-brain barrier to exert their therapeutic effects in the brain compartment.**
- **With a view of surmounting this obstacle, Angiochem has developed a new vector technology based on chemically attaching any size molecule to one of a family of peptides in order to access the brain.**
- **ANG1005, an Angiopep-2/paclitaxel conjugate, is the first entity using this technology to be tested in humans. Clinical safety and tolerability data to date provide new hope to those dealing with brain cancers and, in future, possibly other brain diseases.**