Phase 2 Study of Aldoxorubicin in Relapsed Glioblastoma

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Abstract

Background: Glioblastoma (GBM) is the most common primary brain tumor with a median survival of ~14 months after initial therapy. Relapsed patients usually receive bevacizumab with an ORR of~20%, and OS of ~31 weeks. Recently Prakash et al demonstrated in an orthotopic mouse model of GBM that IV aldoxorubicin (A) but not doxorubicin (D) significantly delayed tumor growth and prolonged survival by over 100%. D does not penetrate the blood-brain barrier. A is a prodrug of D that is attached to a pH sensitive linker that binds covalently to albumin and is released preferentially within tumors. We assessed the preliminary efficacy and safety of A administered to GBM patients who progressed after first line therapy. **Methods:** Patients > 18 yrs with 1st relapse GBM received either 250 mg/m^2 (21) or 350 mg/m^2 (7) every 21 days until tumor progression, unacceptable toxicity or withdrawal. Tumors were assessed every 6 weeks by MRI and in some instances Dynamic Susceptibility Contrast (DSC) MRI. Safety monitoring included serum chemistries and CBC prior to each infusion and echocardiograms every 2 months. **Results:** Median age was 56 yrs (28-73); 19 females and 9 males. Subjects received 1-20 cycles of treatment. Median drug exposure for the 250 mg/m^2 dose is 1042 mg/m^2 D equivalents (Deq) (range 371-5768 mg/m^2 Deq) and for the 350 mg/m^2 dose is 1912 mg/m^2 Deq (range 472-3647 mg/m^{2}Deq). Best responses in 21 subjects according to MRI were 3 PR, 7 SD and 11 PD. Median overall survival has not been reached (range is 0.5-17.3+ months) with median f/u of 7 months (1-17+ months). Major grade 3 or 4 AEs include neutropenia (6 subjects) febrile neutropenia (2 subjects) mucositis (2 subjects), thrombocytopenia (2 subjects) and anemia (2 subjects). 2 subjects experienced treatment-related SAEs. No subjects had a decrease in their LVEF below 50% of expected values. Two subjects with apparent PD by scan underwent tumor debulking and had no microscopic evidence of disease. Another subject demonstrated no active malignancy upon DSC MRI scanning. **Conclusions:** Unlike doxorubicin, aldoxorubicin appears to penetrate the blood-brain barrier in humans and is associated with objective tumor responses, stable disease and prolonged survival. Pseudoprogression occurs and may confuse responsiveness to A.

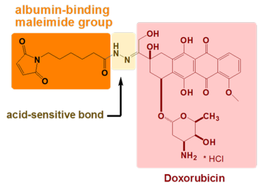
Background

- GBM is the most common and aggressive of all primary brain tumors. Approximately 12,500 gliomas of all grades are diagnosed in the US each year, and GBM accounts for over 60% of these malignancies.[1] Without treatment, survival is only approximately 3 months.[2]
- Therapies involving surgery, radiation plus concurrent and adjuvant temozolomide chemotherapy extend survival to a median of 14 months, with PFS of around 7 months. Unfortunately, virtually all patients relapse regardless of the initial therapy administered.[3]
- Marrero et al., demonstrated in an orthotopic mouse model of GBM that IV aldoxorubicin, but not doxorubicin significantly delayed tumor growth and prolonged survival by over 100%. [4]

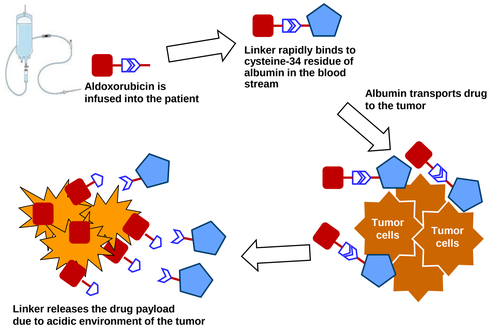
Aldoxorubicin

- Aldoxorubicin is a prodrug of the anticancer agent doxorubicin which is derivatized at its C-13 keto-position with a thiol-binding spacer molecule (6-maleimidocaproic acid hydrazide).
- Aldoxorubicin is quantitatively and selectively bound to the cysteine-34 position of endogenous albumin within a few minutes of administration. The reaction follows second-order kinetics.
- Aldoxorubicin was superior to free doxorubicin in several human tumor xenograft models and in low dose combination studies.[5]
- Toxicological studies in mice, rats, and dogs demonstrated a 3- to 5-fold increase in the MTD, moderate and reversible myelosuppression, no liver toxicity and immunotoxicity, and no new toxicity compared to doxorubicin.[6]
- Aldoxorubicin is significantly less cardiotoxic in a chronic rat model when compared to doxorubicin at an equitoxic dose.[7]

Structure of Aldoxorubicin



Proposed Mechanism of Action



Objectives

Primary

- The primary objective of this study is to determine the preliminary efficacy of administration of aldoxorubicin to subjects with unresectable GBM whose tumors have progressed following treatment with surgery, radiation and temozolomide, as measured by PFS according to the RANO Working Group Criteria and OS.

Secondary

- To evaluate the safety of aldoxorubicin in this patient population.

Study Design

- Aldoxorubicin was administered to 2 cohorts at doses of 250 mg/m^2 and 350 mg/m^2 (185 and 260 mg/m^2 doxorubicin equivalents, respectively) IV on Day 1 every 21 days until tumor progression, unacceptable toxicity, or consent was withdrawn.
- Safety assessments including adverse events, physical exam, serum chemistry, CBC, urinalysis, and ECG were performed at each visit.
- Cardiac function was assessed by Echocardiography.
- Tumor response was monitored every 6 weeks by an independent radiology contract research organization using the RANO Working Group criteria.

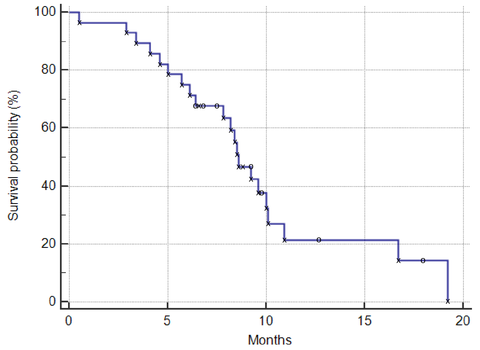
Key Eligibility Criteria

- Age ≥ 18, male or female.
- Histologically or cytologically confirmed unresectable GBM. Subjects with recurrent disease whose prior pathology demonstrated GBM will not need to be re-biopsied. Subjects with prior low-grade glioma or anaplastic glioma are eligible if histological assessment demonstrates transformation into GBM.
- Cancer progression after treatment with the following: surgery, radiation therapy and temozolomide with no other therapy prior to tumor recurrence.
- Karnofsky performance status ≥ 70.
- Life expectancy ≥ 8 weeks.
- No prior exposure to an anthracycline.

Patient Characteristics

Characteristics	250 mg/m^2	350 mg/m^2
N	21	7
Age, median (range)	56 (39-72)	55 (28-73)
Male / Female, # (%)	13 (60) / 8 (40)	6 (86) / 1 (14)
Race, # (%)		
Caucasian	19 (90)	6 (86)
Black or African American	1 (5)	0
Asian	0	1 (14)
Native Hawaiian or other Pacific Islander	1 (5)	0
Karnofsky, median (range)	90 (70-100)	90 (70-100)
Prior Chemo Regimens, median (range)	2 (1-3)	1 (1-2)
Completed Cycles, median (range)	3 (1-20)	4 (1-7)
Aldoxorubicin Dose/Cycle, median mg (range)	490 (378-668)	669 (416-970)
Doxorubicin Dose/Cycle, median mg (range)	364 (280-496)	497 (309-720)
Aldoxorubicin Cumulative, median mg (range)	1608 (525-7,748)	2574 (637-4,909)
Doxorubicin Cumulative, median mg (range)	1194 (390-5,756	1912 (473-3,647)

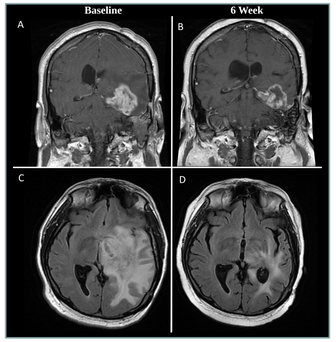
Preliminary Kaplan-Meier Survival Curve – Across Doses



X: death; 0:censored

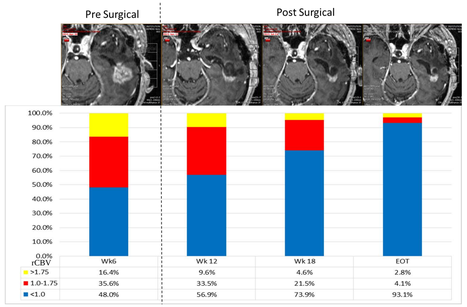
As of 15APR2016
1. Median OS = 8.6 months (95% CI: 7.8-10.1)
2. Number of patients alive = 7
3. 68% of subjects went on to Avastin

Representative Scans



Treatment effects of aldoxorubicin in recurrent GBM (left temporal lobe). Baseline (panels A and C) and 6 week follow-up (panels B and D) post gad T1W MRI scans demonstrates tumor shrinkage (26.2% reduction in bidimentional measurements) with improvements in L→R midline shift and mass effect upon the lateral ventricles. (panels A and B) There is also a significant reduction in T2 Flair signal (panels C and D).

Fractional Tumor Burden Estimates Based Upon DSC MRI Results



rCBV	Wk6	Wk 12	Wk 18	EOT
>1.75	16.4%	9.6%	4.6%	2.8%
1.0-1.75	35.6%	33.5%	21.5%	4.1%
<1.0	48.0%	56.9%	73.9%	93.1%

Role of relative Cerebral Blood Volume (rCBV) as a measure of non-tumor T1W Gad Enhancement (pseudoprogression). Dynamic susceptibility contrast (DSC MRI) is a Post Gad T1W sequence that measures the volume of blood in enhancing tissues to distinguish tumor perfusion (rCBV ≥ 1.0) from inflammation (rCBV <1.0). Shown above is a subject who underwent surgical resection for progression during aldoxorubicin treatment. The bar graph demonstrates that 48% of enhancing pixels within the tumor were in the non tumor enhancement (pseudoprogression) range confirmed by pathology (approximately 60% necrosis). Following surgery, the subject continued on aldoxorubicin therapy with continued reduction of tumor like enhancement. The yellow bars demonstrate most aggressive areas of tumor enhancement by DSC MRI.

Several subjects, despite radiological evidence of progression, underwent debulking surgery. Pathological assessment demonstrated no viable cancer tissue in debulked tissue.

Grade 3/4 Treatment Emergent Adverse Events

(related to aldoxorubicin; > 1 event)

	250 mg/m^2		350 mg/m^2	
	N=21		N=7	
	No. (%)		No. (%)	
Event	**Gr. 3**	**Gr. 4**	**Gr. 3**	**Gr. 4**
Neutropenia	1 (5)	2 (10)	1 (14)	4 (57)
Febrile neutropenia	2 (10)			
Thrombocytopenia		1 (5)	1 (14)	
Mucositis	1 (5)		1 (14)	
Fatigue	1 (5)		1 (14)	
Decreased WBC		1 (5)		3 (43)

Cardiac Evaluation

% subjects with >10% decrease in LVEF	16% (3/19)*
% subjects with >10% increase in LVEF	5% (1/19)
% subjects with LVEF <55%	16% (3/19)
% subjects with QTc >500 msec	4% (1/28)**

*only patients with 1 post-dose ECHO; **none deemed clinically significant by investigators

Serious Adverse Events

- Aldoxorubicin-related SAEs included febrile neutropenia (1), mucositis (1), oral candidiasis (1), somnolence (1), seizure (1). No treatment-related deaths occurred.

Conclusions

- Aldoxorubicin treatment at 250 mg/m^2 every 3 weeks appears to be safe and relatively well-tolerated, and demonstrated anti-tumor activity in patients with relapsed GBM.
- Pseudoprogression appears to be commonly associated with this therapy.
- Binding to albumin appears to allow doxorubicin to cross the blood-brain barrier and enter tumors.
- No evidence of CNS toxicity of aldoxorubicin was observed.
- Combination of aldoxorubicin with bevacizumab may enhance uptake and activity of these drugs in GBM patients.

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