A RANDOMIZED, CONTROLLED TRIAL OF BERUBICIN, A NOVEL TOPOISOMERASE II INHIBITOR, AFTER FIRST-LINE THERAPY FOR GLIOBLASTOMA MULTIFORME (GBM): UPDATED RESULTS

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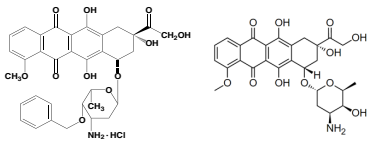
ABSTRACT TIPS-20

Abstract

Berubicin is a doxorubicin (Dox) analog with significant central nervous system (CNS) uptake. Berubicin prolongs survival in orthotopic mouse intracranial models with greater infiltration of the tumor compared to normal tissue.



Berubicin

Doxorubicin

A Phase 1 dose-escalation enrolled thirty-five patients with recurrent or refractory GBM or other primary brain cancers to receive IV Berubicin over 2 hours for 3 consecutive days (one cycle) every 21 days. Doses were escalated using an accelerated titration design and ranged from 1.2 to 9.6 mg/m^2/day.

The most common dose limiting toxicity (DLT) was myelosuppression, more specifically neutropenia. Minimal nonhematological toxicities were observed, no neurotoxicity or cardiotoxicity was noted. The maximum tolerated dose (MTD) was 7.5 mg/m^2/day.

Of 25 patients evaluable for efficacy, one patient demonstrated a Complete Response (CR) and is in remission >15 years; 2 patients had partial/minor responses; 9 patients had stable disease leading to an overall 48% clinical benefit rate.

Multicenter, Open-Label Study with a Randomized Control Arm of the Efficacy, Safety, and Pharmacokinetics of Intravenously Infused Berubicin in Adult Patients with Recurrent GBM (WHO Grade IV) After Failure of Standard First Line Therapy

A trial of Berubicin vs Lomustine in patients with recurrent GBM (IDH WT) after first-line therapy in the US and EU is enrolling patients in a 2:1 randomization design of Berubicin:Lomustine. Patients will be stratified by MGMT methylation status. The primary objective is to assess the effect of Berubicin compared with Lomustine on the primary endpoint of overall survival (OS) in adult patients with GBM after standard initial therapy. An interim futility analysis to explore the relative efficacy between these drugs will be conducted after up to half of the patients have reached 6 months of therapy.

As of the data cutoff of 17October2022, 49 patients have been enrolled; 35 on Berubicin and 14 on Lomustine.

Patient Demographics*

Parameter	Berubicin n=105	Lomustine n=46	Overall n=151
Age (years) Mean (SD)	57.1(13.1)	58.9(10.8)	57.6(12.5)
Male n (%) / Female n (%)	70 (66.7)/ 35 (33.3)	33 (71.7)/ 13 (28.3)	103 (68.2) /48 (31.8)
Race n (%)			
White	81 (77.1)	34 (73.9)	115 (76.2)
Black or African American	3 (2.9)	1 (2.2)	4 (2.6)
Asian or Pacific Islander	5 (4.7)	2 (4.3)	7(4.6)
Not Reported or Unknown	16 (15.2)	9 (19.6)	25(16.6)
BSA (m^2) Mean (SD)	1.98 (0.24)	2.00 (0.27)	1.98 (0.25)
MGMT methylation n (%)	40 (38.1)	18 (39.1)	58 (38.4)
Baseline KPS Mean (SD)	85.6 (10.60)	82.0 (8.85)	84.5 (10.20)

Patient Disposition

Parameter	Berubicin n=105	Lomustine n=46	Overall n=151
Completed Study n (%)	55 (52.4)	21 (45.7)	76 (50.3)
Continuing on study n (%)	40 (38.1)	17 (37.0)	57 (37.7)
Withdrew from the study n (%)	10 (9.5)	8 (17.4)	18 (11.9)
Primary Reason for Withdrawing n (%)			
Adverse Event	2 (1.9)	2 (4.3)	4 (2.6)
Physician Decision	1 (1.0)	1 (2.2)	2 (1.3)
Withdrawal by Patient	5 (4.8)	4 (8.7)	9 (6.0)
Death	1 (1.0)	0	1 (0.7)
Other	1 (1.0)	1 (2.2)	2 (1.3)

Adverse Events (≥ 10%)

Preferred Term	Berubicin n=105		Lomustine n=46		Overall n=151	
	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
Any Reported	88 (83.8)	49 (46.7)	39 (84.8)	18 (39.1)	127 (84.1)	67 (44.4)
Anaemia	14 (13.3)	2 (1.9)	6 (13.0)	0	20 (13.2)	2 (1.3)
Asthenia	11 (10.5)	3 (2.9)	6 (13.0)	0	17 (11.3)	3 (2.0)
Constipation	10 (9.5)	0	5 (10.9)	0	15 (9.9)	0
Fatigue	28 (26.7)	0	9 (19.6)	0	37 (24.5)	0
Headache	18 (17.1)	6 (5.7)	3 (6.5)	1 (2.2)	21 (13.9)	7 (4.6)
Lymphocyte count decreased	14 (13.3)	9 (8.6)	10 (21.7)	6 (13.0)	24 (15.9)	15 (9.9)
Nausea	18 (17.1)	0	11 (23.9)	0	29 (19.2)	0
Neutrophil count decreased	21 (20.0)	9 (8.6)	7 (15.2)	2 (4.3)	28 (18.5)	11 (7.3)
Platelet count decreased	5 (4.8)	2 (1.9)	14 (30.4)	4 (8.7)	19 (12.6)	6 (4.0)
Seizure	10 (9.5)	5 (4.8)	7 (15.2)	3 (6.5)	17 (11.3)	8 (5.3)
Thrombocytopenia	1 (1.0)	0	4 (8.7)	1 (2.2)	5 (3.3)	1 (0.7)
White blood cell count decreased	13 (12.4)	8 (7.6)	9 (19.6)	3 (6.5)	22 (14.6)	11 (7.3)

Updated Results:

All patients enrolled show comparable demographics within each arm, including age, gender, race, BSA and KPS. In addition, patients with unmethylated MGMT are approximately 38-39%, allowing for a reasonable comparison of efficacy irrespective of the arm of the study. Although slightly more patients have completed the study on the Berubicin arm, there are a comparable percentage that are continuing on the study.

All grades of adverse events occurring in more than 10% of patients, as well as Grade 3-5 events, are shown to be relatively similar in the Berubicin and Lomustine arms. In terms of myelosuppression (lymphocyte, neutrophil and red blood cell [anemia] reductions.

Although this data remains incomplete, we are continuing our evaluation of efficacy and will provide an interim analysis (futility score) of overall survival between these treatment arms when we have 30-50% of patients on the study and 44 events (deaths) based on this study evaluating the primary endpoint (Overall Survival). The ultimate outcome of this trial is to potentially provide therapeutic options for patients after first-line therapy.

Information provided is preliminary and has not been validated or certified