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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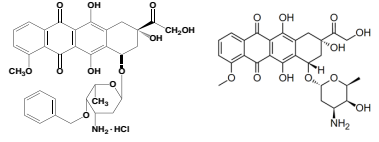
ABSTRACT TIPS-20

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 study 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; 1 patient had an unconfirmed Partial Response (PR) and 10 patients had Stable Disease (SD) leading to an overall 44% 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 to 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 been enrolled and when there are 44 events (death).

As of the data cutoff of 30 June 2023, 151 patients have been enrolled; 105 on Berubicin and 46 on Lomustine. Note that numbers may have changed from a previous presentation due to updating the database and quality controls.

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 for each arm, including age, gender, race, BSA and KPS. In addition, patients with unmethylated MGMT are approximately 38%, allowing for a reasonable comparison of efficacy irrespective of the arm of the study and impact of this baseline. Approximately 50% of patients on both arms have completed the study, i.e. have participated in an end of treatment(EOT) visit, and withdrawal prior to EOT is relatively small, although almost twice the percent of patients in the Lomustine group compared to Berubicin have withdrawn, with the reasons provided.

All grades of adverse events occurring in more than 10% of patients, as well as Grade 3-5 events, are shown in the final table, with the overall percentages similar in the Berubicin and Lomustine arms. In terms of myelosuppression (lymphocyte, neutrophil, white blood cell and red blood cell count [anemia] reductions are also similar however thrombocytopenia seems to be higher in the Lomustine arm.

We are continuing our evaluation of efficacy and will provide an interim analysis of overall survival between these treatment arms when 30-50% of patients have been on the study and we have seen 44 events (deaths). The ultimate outcome of this trial is to provide an effective and well-tolerated therapeutic option for patients with Glioblastoma after first-line therapy.

Information provided is preliminary and has not been validated or certified