A phase I, pharmacokinetic (PK) study of MBP-426, a novel liposome encapsulated oxaliplatin

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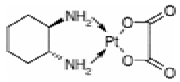
Abstract

Background:
MBP-426 is a novel liposome encapsulated oxaliplatin (L-OHP) formulation bound to human transferrin, developed to improve the safety and efficacy of L -OHP through the prolongation of circulation time and by targeting transferrin receptors on tumor cells. In vitro, MBP-426 is effective against various human cancer cell lines. This study assessed the toxicity and safety of intravenously (IV) administered MBP-426, including defining the maximally tolerated dose (MTD), dose-limiting toxicities (DLTs), and pharmacokinetics (PKs).
Methods:
Patients (pts) with advanced/ metastatic solid tumors refractory to conventional therapy received MBP-426 as 2-4 hrs IV infusion every 3 weeks in cohorts of 3 to 6 pts. Enrollment required age > 18 yrs, ECOG Performance Status 0-2 and adequate organ functions. Tumor response was assessed by RECIST. Plasma was sampled for PK.
Results:
39 pts were dosed, median age 59 (range 27-79), 25 (64%) male. The common tumor types were colorectal 23 (60%), pancreas 3 (8%), and neuroendocrine 3 (8%). Most pts were heavily pretreated with chemotherapy or chemoradiation. 77% pts had received oxaliplatin or cisplatin. Eleven dose levels ranging from 6 to 400 mg/m² were evaluated. At 400 mg/m², 2/3 pts had DLT as grade 4 thrombocytopenia and prolonged thrombocytopenia (1 pt each). The recommended phase II dose is 226 mg/m² where 1/6 pts had grade 4 thrombocytopenia. Grade 3-4 toxicities included fatigue (3 pts), hypercholesterolemia (3 pts), anemia (2 pts) and constipation (1 pt). Common grade 1-2 toxicities were nausea and/or vomiting (59%), fatigue (43%), infusion reaction (15%), thrombocytopenia (15%), anemia (13%) and peripheral neuropathy (13%). 15 pts had stable disease after 2 cycles. 3 pts with colon carcinoma refractory to conventional oxaliplatin had stable disease for 4, 5 and 6 cycles respectively, one of them had 25% decrease in target lesions. PKs of MBP-426 were dose-proportional. Main PK parameters at 226 mg/m² were AUC 2141±419 μg.hr/ml, and t½ 89±92 hr, comparing favorably with intact L-OHP.
Conclusions:
MBP-426 has a favorable safety profile with thrombocytopenia as main DLT. The PK target concentration of L-OHP was exceeded at higher doses. Based on PK and toxicity profiles, the recommended dose is 226 mg/m².

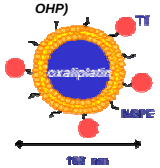
Background

The transferrin-conjugated liposomal oxaliplatin formulation MBP-426 was developed to improve the safety and efficacy of oxaliplatin through the prolongation of drug circulation time in plasma and thus bioavailability and by targeting transferrin receptors on tumor cells.

MBP-426 has shown antitumor effect as evaluated in the human xenograft tumor models: MX-1 (breast carcinoma), HCT-116 (colon carcinoma), HT-29 (colon carcinoma), MKN45 (gastric carcinoma) and COLO-205 (colon carcinoma).



Oxaliplatin (*L-OHP*)



MBP-426 is transferrin-NG-DOPE liposome, encapsulated oxaliplatin

Objectives

Primary
•To assess the toxicity and safety profile of MBP-426 including the determination of the MTD, DLT and recommended phase II dose
•To perform Pharmacokinetic (PK) analysis of MBP-426 given by continuous intravenous infusion.

Secondary Objectives:
•To assess the anti-tumor activity of MBP-426 given continuous intravenous infusion.

Exploratory Objectives
• To evaluate the correlation between antitumor activity and blood transferrin levels, iron saturation status, circulating tumor cells, and/or transferrin receptor expression in archived tumor material.

Methods

Major Inclusion Criteria
• Have pathologically-confirmed malignancy that is locally advanced or metastatic solid tumor and is refractory to standard therapy or for which conventional therapy is not reliably effective or no effective therapy is available.
•ECOG Performance Status of 0, 1, or 2.
• Have adequate clinical laboratory values (i.e., absolute neutrophil count ≥ $1.5x10^9$ mg/L; platelets ≥ $100x10^9$ mg/L; serum creatinine ≤1.5 x upper limit of normal for the institution; creatinine clearance (calculated) > 60 mL/min (using the Cockcroft-Gault equation); bilirubin ≤1.5 x ULN, alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN; patients with known liver metastases may have up to 5 times ULN AST and ALT levels).

Major Exclusion Criteria
•Previous anticancer chemotherapy, immunotherapy, radiotherapy, or any other investigational therapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study entry.
•Extensive prior radiotherapy on more than 30% of bone marrow reserves or prior bone marrow/stem cell transplantation.
• Concomitant malignancies of another type, with the exception of adequately treated in situ cervical cancer and basal cell skin cancer or have demonstrated no evidence of disease for 5 years or more.
•Patients that have a hematologic malignancy.
•Patients with > Grade 1 peripheral neuropathy.
•Patients having history of allergic reactions to platinum-based or liposomal agents.

Results

Patient Baseline Demographics and Disease Characteristics (n=39)

Demographics	n=39
Median Age (Years)	60
ECOG Performance status	
•0-1	37
•2	2
Male, n (%)	25 (64%)
Female, n (%)	14 (36%)
Caucasian, n (%)	29 (74%)
Black, n (%)	3 (18%)
Hispanic, n (%)	7 (8%)
Prior Chemotherapy:	
•≤ 3 prior regimens, n (%)	16 (41%)
•≥ 4 Prior regimens, n (%)	23 (59%)
Prior Radiation Therapy:	6 (15%)
Tumor Types:	
Colorectal CA, n (%)	23 (60%)
Pancreatic CA, n (%)	3 (8%)
Other, n (%)	13 (32%)

Results

MBP-426 Dose levels	Number of patients		Total number of cycles	Patients with DLT	
mg/m²	New to level	Dose reduction		First Cycle	All Cycles
6	3	0	11	0/3	0/3
12	3	0	5	0/3	0/3
24	3	0	10	0/3	0/3
48	3	0	5	0/3	0/3
64	3	0	7	0/3	0/3
96	3	0	13	0/3	0/3
128	3	0	6	0/3	0/3
170	3	0	22	0/3	0/3
226	6	0	10	1/6	1/6
301	3	2	6	0/3	0/3
400	6	0	8	2/6	2/6

Safety profile

System organ class	Grade 1-2		Grade 3-4		All No.(%)
Hematological Adverse events	No. of patients	Percent	No. of patients	Percent	
Anemia	3	7.7	2	5.1	5 (12.8)
Neutropenia	3	7.7	0	0	3 (7.7)
Thrombocytopenia	1	2.6	4	10.3	5 (12.8)
Non-hematological Adverse events					
Nausea	22	56.4	0	0	22 (56.4)
Vomiting	10	25.6	0	0	10 (25.6)
Fatigue	14	35.9	3	7.7	17 (43.6)
Hypercholesterolemia	2	5.1	3	5.1	5 (12.8)
Infusion reaction	6	15.4	0	0	6 (15.4)
Peripheral neuropathy	3	7.7	0	0	3 (7.7)
Anorexia	4	10.3	4	10.3	4 (10.3)
Constipation	3	7.7	1	2.6	4 (10.3)

Efficacy

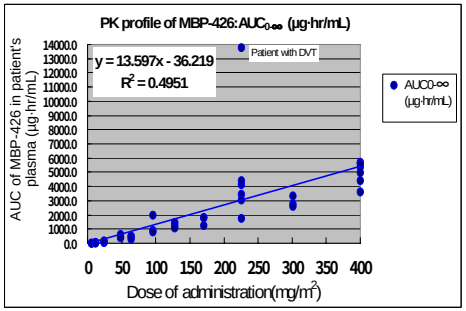
• 15 patients had stable disease after 2 cycles
• 3 pts with colon carcinoma refractory to conventional oxaliplatin had stable disease for 4,5 and 6 cycles respectively
• Two patients had 12% and 26% decrease in target lesions respectively

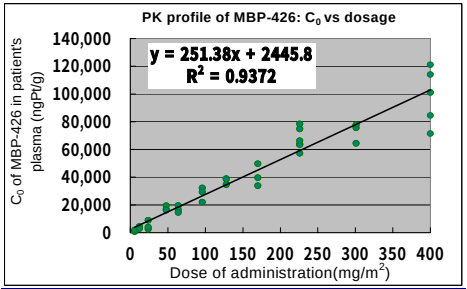
Pharmacokinetics

PK parameters of MBP-426

Cohort (mg/m²)	C_0(μgPt/g)	$AUC_{0\text{-}inf}$ (μg·hr/mL)	t½ (hr)	CL (ml/m²/hr)	V_{ss} (mL/m²)
6	1.25 ± 0.64	13.4 ± 7.5	45.6 ± 8.5	542.6 ± 257.5	27784.8 ± 23838.2
12	3.76 ± 0.80	43.2 ± 22.4	28.5 ± 12.7	360.2 ± 244.7	9559.2 ± 9192.4
24	5.18 ± 3.29	85.1 ± 82.2	39.8 ± 10.0	469.7 ± 291.5	18185.6 ± 13699.1
48	17.5 ± 1.6	476.5 ± 135.2	36.2 ± 26.8	105.7 ± 26.0	4319.9 ± 1883.1
64	16.9 ± 2.5	423.3 ± 108.3	23.9 ± 7.6	159.1 ± 46.3	4271.4 ± 517.4
96	21.8 ± 7.6	1206.8 ± 653.6	26.4 ± 9.1	93.7 ± 39.6	2990.4 ± 305.2
128	37 ± 2.4	1258.1 ± 208.1	24.6 ± 8.4	103.6 ± 17.0	3497.1 ± 1051.2
170	43.5 ± 8.5	1609.4 ± 327.3	34.5 ± 5.0	109.0 ± 25.1	4741.9 ± 297.4
226	67.3 ± 7.8	5095.9 ± 4354.6	89.1 ± 92.5	65.0 ± 36.4	4771.1 ± 1555.3
301	72.6 ± 7.2	2906.6 ± 396.0	27.3 ± 1.4	104.8 ± 13.5	3808.3 ± 110.2
400	98.8 ± 18.4	4940.8 791.2	53.8 ± 46.5	83.0 ± 15.2	5903.7 ± 5108.4

Correlation of administration dose(mg/m²) with AUC_{inf} and C_0: The Dose dependent linearity of PKs in plasma





Conclusions

• MBP-426 has an acceptable safety profile at the dose level of 226 mg/m² every three weeks and this level appears to be the MTD
• DLT was thrombocytopenia at the dose level of 400 mg/m².
• PK analysis showed dose dependent increase in AUC and C_0
• Tumor volume reduction was noted in two patients and stable disease over time in others, suggestive of preliminary activity.
• Majority of these patients had prior exposure to oxaliplatin or cisplatin.