

A Phase I and Pharmacokinetic (PK) Trial of AP5346, a Novel Polymer-Linked DACH Platinum (Pt) Compound, Administered as an Intravenous (IV) Infusion Once a Week for 3 Consecutive Weeks in Advanced Solid Tumor Patients

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1. Background

AP5346 is a macromolecular carrier linked to a bioactive DACH-platinum complex. The macromolecular carrier is a water soluble biocompatible 90:10 random copolymer of a N-(2-hydroxypropyl)methacrylamide (HPMA) monomer and a methacrylamide monomer substituted with a tri-glycine group, the linker to the platinum complex (Figure 1).

AP5346 was designed to take advantage of the enhanced permeability and retention effect, in which tumor neovasculature shows greater permeability to macromolecules than normal tissue, often associated with limited lymphatic and/or capillary drainage. The DACH-platinum complex is thought to be biologically inert while attached to the polymer, with slow in vivo release accelerated by low pH environments, such as the extracellular space of hypoxic tumors and the intracellular lysosomal compartment.

AP5346 produced greater tumor growth inhibition and prolonged growth delay compared to equitoxic oxaliplatin and/or carboplatin doses in B16 melanoma, 2008 ovarian, HT-29 colorectal, and Lewis lung tumor models.

We have undertaken the first phase I trial in solid tumor patients of AP5346 administered weekly over 1 hour, for 3 weeks out of every 4 weeks.

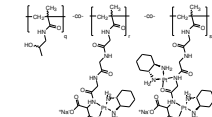
2. Study Objectives

- To determine the maximum tolerated dose (MTD) of a course of 3 weekly 1 hr infusions of AP 5346 given on days 1, 8 and 15 every 4 weeks;
- To establish a recommended dose for phase II trials on this dose schedule;
- To determine the qualitative and quantitative toxic effects of 3 weekly 1 hr infusions of AP 5346 and to study the predictability, duration, intensity, onset, reversibility and dose-relationship of the toxic side effects.

Secondary Objectives

- To determine the pharmacokinetics of total and ultrafiltrable platinum and circulating WBCs DNA adduct levels as a function of AP 5346 dose;
- To document possible antitumor activity;
- To measure the level of platinum-DNA adducts in tumor sample 24 hours after the first dose of AP 5346.

Figure 1. Partial chemical structure of AP5346, a random copolymer, where q:r:s is approximately 36:47:23:1



3. Study Design

Open label, dose-finding phase I study conducted in 2 centers in France and Holland

Administration schedule

AP5346 was administered in a 1-hour IV infusion in 500 mL of 5% glucose once per week for 3 weeks with a 1 week rest.

Dosing on days 8 or 15 was omitted in case of grade 3 thrombocytopenia, neutropenia, or leukopenia

Anti-emetic prophylaxis was not mandated by the protocol, but, from DL 5, 5-HT₃ antagonists and corticosteroids were administered prophylactically to most patients.

The following hydration and urine alkalization scheme was applied in DL 5-7

Prehydration (immediately prior to infusion)	No bisphosphonate 2000 mL 1.4% IV 12 hr
Posthydration (immediately post-infusion)	No bisphosphonate 2000 mL 1.4% IV 20-22 hr
Day 2 (until next infusion)	No bisphosphonate 1000 mg p.o. 4, 6, 8, 10
Rescue if pH < 7 in 24 hours after infusion	No bisphosphonate 100 mL 4.2% or 50 mL 8.4% IV

Planned Dose Escalation Scheme

The starting dose was 40 mg Pt/m², one-tenth of the MTD in the most sensitive species (leishia miki). The magnitude of dose escalation with successive dose levels was determined according to the severity of toxicity in preceding DL, as follows:

Maximum NCI-CTC grade of toxicity by prior DL	Dose Escalation	Initial number of patients per DL
None/grade 1	100%	1
2	or 1	3
3, 4	or 2, 4	20% - 33%

* except anemia
 † except alopecia and untreated nausea/vomiting

In the event of DLT during cycle 1, a total of 6 patients were to be entered in that dose level.

Definition of DLT

DLT was defined as any of the following treatment-related toxicities:

- Non-hematologic toxicity grade 3-4 (except inadequately treated nausea/vomiting);
- Neurotoxicity grade 2 lasting > 2 weeks;
- Neutropenia grade 4 lasting > 5 days or complicated by fever or infection;
- Thrombocytopenia grade 4;
- The inability to receive 3 weekly consecutive doses of the drug for reasons of toxicity which in itself are not dose-limiting, but might become dose-limiting if administrations would continue
- Delay of cycle 2 by > 2 weeks

Definition of MTD

The MTD was defined as the DL in which ≥ 2/6 patients experienced a DLT during the first cycle of therapy.

The RD was to be one dose level below the MTD

4. Principal Eligibility Criteria

• Histological or cytologically confirmed advanced solid tumor not amenable to standard treatment

• WHO Performance Status 0-2

• Age ≥ 18 years

• Adequate hematological and biochemical function

• Bone marrow: Absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/L; platelet count ≥ 100 x 10⁹/L

• Hepatic: Total serum bilirubin ≥ 1.5 x the upper limit of normal (ULN); alkaline phosphatase (AP), AST and ALT ≥ 3 x ULN

• Renal: serum creatinine, blood urea ≤ 1 x ULN, calculated creatinine clearance > 50 mL/min (Cockcroft and Gault)

• Absence of clinical signs of brain metastases and/or leptomeningeal involvement

• Neuropathy ≥ CTX grade 2, or hearing loss ≥ CTX grade 2.

• No prior nephrectomy.

• Signed informed consent

5. Pharmacokinetics

Pharmacokinetic samples were taken in all treated patients on day 1 of cycle 1, at the following time points: prior to infusion, and 0, 15, 30 min, 1, 2, 4, 7, 24, 48, 96 hours after the end of the infusion. Samples were also taken prior to each infusion during first 2 cycles to measure platinum trough levels.

Plasma samples were analyzed by atomic absorption spectrophotometry for total platinum and ultrafiltrable platinum (<3 kDa), with a lower limit of quantitation of 0.1 µg/mL and 0.02 µg/mL, respectively.

Pharmacokinetic parameters were calculated using WinNonlin ver 3.1 by non-compartmental methods.

6. Results

Between April 2003 and December 2004, 26 patients were treated in 7 dose levels

Dose level	Dose per infusion (mg Pt/m ²)	Number of patients		
		Treated	Evaluable for MTD	Evaluable for safety
1	40	1	1	1
2	60	1	1	-
3	160	3	2	3
4	200	3	3	2
5	640	6	6	6
6	850	6	6	4
7	1200	6	6	4
Total		26	24	17

Patient Characteristics	DL 1-7							Total
	DL 1-3	DL 4	DL 5	DL 6	DL 7	DL 7	Total	
Number of patients treated	5	3	3	3	6	6	15	26
Sex								
Female	4	1	3	3	4	4	14	
Male	2	2	0	0	2	2	12	
Median age (range)	61 (53-72)	61 (43-70)	66 (50-80)	46 (34-74)	59 (35-74)	53 (34-74)	53 (34-74)	
Performance status (WHO)								
0	1	2	5	1	3	11		
1	4	1	1	5	3	13		
2	1	1	1	1	2	4		
History								
Brain	3	1	1	1	2	5		
Diabetes	1	1	1	1	2	4		
Ovarian	2	1	1	1	2	4		
Other*	2	1	1	1	2	4		

Prior chemotherapy	DL 1-7							Total
	DL 1-3	DL 4	DL 5	DL 6	DL 7	DL 7	Total	
No. involved sites	2	1	1	2	3	3	12	
1-4	(1-4)	(2-4)	(1-5)	(2-5)	(2-4)	(1-5)		
Involved sites								
Lymph Nodes	4	4	3	3	3	3		
Lung	2	2	3	5	5	17		
Liver	1	1	4	2	3	11		
Bone	2	1	4	1	1	8		
Primary Tumor	1	1	2	3	1	8		
Other*	5	3	2	6	4	20		

* ACUP, cervix, esophageal, NSCLC, pancreatic, prostate, renal, thyroid, Ewing sarcoma, urachus, peritoneal carcinoma
 † Pleural effusion, vein, CNS, pericardial effusion, adrenal, kidney, mediastinum, mesenterium.

Treatment exposure and reasons for discontinuation

Number of patients treated	DL 1-7							Total
	DL 1-3	DL 4	DL 5	DL 6	DL 7	DL 7	Total	
Cycles administered	5	3	3	3	6	6	26	
Median in cycles per patient	2 (1-2)	2 (1-2)	2 (1-4)	1 (1)	1 (1-3)	1 (1-4)		
Reason for discontinuation								
Progressive disease	3	1	3	3	1	11		
AE: Treatment related	2	1	3	1	4	13		
AE: Not treatment related	2	1	3	1	2	11		
Patient refusal	1	1	1	1	2	6		
Investigator decision	1	1	1	1	1	4		

Treatment toxicity resulted in 4 cycle delays (DL 1, 5, 7), the omission of 6 infusions (DL 3, 5, 7) and 2 dose reductions (DL 7)

7. Dose Escalation and Determination of MTD

Dose escalation proceeded by 100% dose increments through DL 1 to 5 (640 mg Pt/m²) and 7 (1200 mg Pt/m²). An intermediate DL 6 (850 mg Pt/m²) was subsequently explored.

No DLT was observed during the first cycle in dose levels 1-4

DL 6 was MTD with DLT during the first cycle in 2 out of 5 patients

DL 7 was toxic with DLT in 5 out of 6 patients having a DLT in first cycle

DL 5 is the recommended dose, 1 patient out of 6 having experienced anuria grade 3 accompanied by creatinine elevation grade 4

Dose-limiting toxicity

Dose level (RD)	N patients evaluable	N patients with DLT	Main toxicities
5	5	1	Creatinine elevation gr 4 Anuria gr 3 Fatigue gr 3
6	5	2	Vomiting gr 3
7	6	5	Neutropenic infection gr 4 Diarrhea gr 3 Fatigue gr 3 Hypophosphatemia gr 4 Sicca syndrome gr 3 Renal insufficiency gr 2 Nausea/vomiting gr 3 Neutropenia gr 4 Diabetic keto acidosis Nausea/vomiting gr 3

8. Safety

Two deaths occurred at DL 5 due to renal failure, possibly drug-related. One had not received hydration/urine alkalization prophylaxis and the other had right renal involvement with left renal vein thrombosis

Seven (7) patients (27%) experienced treatment-emergent grade 1-2 creatinine elevation or clearance decrease, without clinical signs of renal dysfunction. Urine alkalization appeared to improve tolerance, with 0% vs 46% grade 2-4 renal toxicity in patients with/without prophylaxis in DL 5-7

70% of patients experienced vomiting, reaching grade 3-4 in 5 patients in DL 5-7 (28%), of whom only 1 had received adequate anti-emetic prophylaxis.

Three (3) patients (12%) reported treatment-emergent grade 1 sensory neuropathy of 1 day duration; no ototoxicity occurred

One (1) case of anaphylactic shock (during the 5th infusion) and a case of urticaria grade 2 (during the 3rd infusion) led to study treatment discontinuation

Until DL 7, neutropenia did not occur and thrombocytopenia was sporadic

Toxicity per patient according to dose level

Toxicity	DL 1-7						
	DL 1-3 (N=15)	DL 4 (N=3)	DL 5 (N=3)	DL 6 (N=3)	DL 7 (N=6)	DL 7 (N=6)	Total (N=26)
Neutropenia	1	1	3	1	1	2	9
Creatinine increased	1	1	2	1	1	4	10
Creatinine clearance decreased	1	1	2	2	1	2	9
Fatigue	1	1	3	1	1	3	10
Nausea	4	1	3	1	4	4	17
Vomiting	4	1	3	1	4	4	17
Abdominal pain	2	1	1	1	1	1	7
Anorexia	2	1	1	1	1	1	7
Diarrhea	2	1	1	1	1	1	7
Neutropenic infection	1	1	1	1	1	1	6
Diabetic keto acidosis	1	1	1	1	1	1	6
Stomatitis	1	1	1	1	1	1	6

Figure 2. Evolution of calculated creatinine clearance during treatment in DL 5-7 in each patient (% change with respect to baseline)

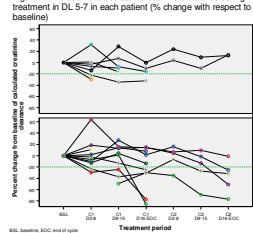
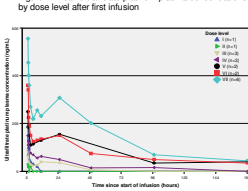


Figure 4. Mean ultrafiltrate platinum plasma concentrations by dose level after first infusion



10. Antitumor Activity

Two partial responses (RECIST criteria) were achieved, in a heavily-pre-treated, platinum-sensitive ovarian cancer patient and in a docetaxel-pre-treated melanoma patient. An ACUP of suspected ovarian origin who was inevaluable due to discontinuation after 2 infusions, had normalization of CA 125 (from 133 U/L), with subsequent sustained response to oxaliplatin with a 52% decrease CA 125 from baseline 83 U/L.

Response DL	Age (year)	Sex	PS	Primary Site	Prior chemotherapy	Metastatic sites	N	TTP (months)
PR	52	F	0	Ovarian	1	lung, LN, ovary	1	3.3
PR	71	M	0	Melanoma	1	lung, LN, skin	1	3.5
SD	47	M	1	Esophageal	6	lung, LN, peritoneum	2	3.3
SD	5	M	0	Melanoma	1	bone, CNS, chest, lung, LN	4	2.8
SD	7	F	0	Cervix	1	lung, LN	1	1.8

11. Conclusions

- The recommended dose for further assessment of AP5346 administered over 1 hour for 3 weeks out of every 4 weeks is 640 mg Pt/m²
- AP5346 was tolerated up to a dose of 640 mg Pt/m², with a toxicity profile characterized by frequent grade 1-2 nausea, vomiting, and creatinine elevations, with an absence of grade 3-4 hematotoxicity below 1200 mg Pt/m².
- Evidence of anti-tumor activity was observed from 640 mg Pt/m², with partial responses achieved in patients with melanoma and ovarian cancer, and disease stabilizations in patients with melanoma, esophageal cancer, and cervix cancer.
- Total and ultrafiltrate platinum Cmax and AUC increased linearly with dose, and terminal half-life did not vary with dose
- Phase II assessment of AP5346 is planned in pre-treated platinum sensitive advanced ovarian cancer patients

12. Reference

1. Johnson S, O'Dwyer P. Cisplatin and its analogues. In: DeVita VT, Hellman S, Rosenberg S, editors. Cancer: Principles & practice of oncology. 7th Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 344-58.

