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Sponsor/company:	Sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00268671
		Study Code:	XRP6976G_2501
Generic drug name:	Docetaxel	**Date:**	29 January 2008

Title of the study:	Phase I/II Trial of Weekly Docetaxel and Cisplatin for Locoregionally Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Protocol number: XRP6976G_2501	
Investigator(s):	Site #1: Dr. Stephen Chia (Coordinating Investigator) BC Cancer Agency, Vancouver Cancer Centre 600 West 10th Avenue Vancouver, BC V5Z 4E6 Site #2: Desiree Hao Tom Baker Cancer Centre (Department of Medical Oncology) 1331-29th Street N.W Calgary, Alberta T2N 4N2	
Study center(s):	2 Canadian sites	
Publications (reference):	No publication	
Study period: Date first subject enrolled: 12-Aug-2003 Date last subject completed: 12-Apr-2006		**Phase of development:** I & II
Objectives:	**Primary objectives** Phase I portion: The objective of the phase I portion was to determine the maximum tolerated doses (MTD) and recommended doses of docetaxel and cisplatin given weekly in combination to subjects with recurrent / advanced SCCHN.	
Methodology:	**Phase I:** Main Inclusion Criteria:	

12 patients diagnosed with locoregional recurrence of histologically confirmed SCCHN of original primary tumor not amenable to curative local therapy or metastatic SCCHN who were eligible for first line palliative systemic therapy. The subjects were required to have measurable disease with ECOG performance status if 0 to 2 inclusive. The subjects were to have adequate bone marrow, hepatic function and renal function with a calculated or measured GFR (glomerular filtration rate) of ≥ 60 ml/min.

Design:

For more details, please refer to the section "Design" for the phase I portion.

Treatment:

Docetaxel was administered intravenously during 30 minutes. An intravenous infusion of cisplatin was delivered after the docetaxel infusion during 30 minutes. No pre-cisplatin or post cisplatin IV hydration was required. Subjects were pre-medicated with dexamethasone 8 mg orally or intravenously. In addition, diphenhydramine at a dose of 50 mg was administrated intravenously 30 minutes before giving docetaxel.

Dose adjustments for toxicity :

Toxic effects were graded using NCI Common Toxicity Criteria version 2.0. Doses were adjusted by worst grade? experienced in previous cycle.

Dose Adjustments for Hematologic Toxicty

Doses are adjusted based on day 1 counts on weekly chemotherapy and/or previous cycle of febrile neutropenia. No dose reductions are performed for nadir counts.

Dose Modification Schedule:

ANC (x 109/L)		Platelets (x 109/L)	Dose (Docetaxel only)
≥ 1.5	And	≥ 100	100%
1.0 – 1.49	And	≥ 100	75% or delay till ANC ≥ 1.5
<1.0	Or	< 100	delay

Dose Adjustments for Non-Hematologic Toxicity

Toxicity	Grade	Action
• Any major organ toxicity	0 - 2	no change
• Any major organ toxicity	3	delay until recovery to < grade 2

	• (except nausea/vomiting) Reduce by one dose level • Any major organ toxicity 4 Off protocol treatment • (except unmedicated nausea/vomiting) If no recovery after 2 weeks, patient goes off protocol therapy **<u>Phase II</u>:** For administrative reasons, the phase II portion of the study was not conducted after a joint decision between the Coordinating Investigator and the Sponsor.		
Number of subjects:	Planned: Phase I: 12 to 15 Phase II: 39 subjects	Randomized: Not applicable	Treated: **Phase I (cycle 1)**: Group 1: 3 patients Group 2: 7 patients Group 3: 3 patients Group 4: 3 patients **Phase II:** None
Evaluated:	Pharmacokinetic (PK): Limited PK was performed as this was a new schedule with weekly docetaxel and cisplatin.	Safety: Adverse events and routine laboratory data were used.	
Diagnosis and criteria for inclusion:	Subjects with a locoregional recurrence of histologically confirmed SCCHN of original primary tumor not amenable to curative local therapy or metastatic SCCHN who were eligible for first line palliative systemic therapy. The subjects were required to have measurable disease with ECOG performance status if 0 to 2, inclusive. The subjects were also to have adequate bone marrow, hepatic function and renal function with a calculated or measured GFR (glomerular filtration rate) of ≥ 60 ml/min.		

Investigational product:	Docetaxel and Cisplatin
Dose:	**Phase I:** Dose level 1: Docetaxel: 25 mg/m^2 Cisplatin: 20 mg/m^2 Dose level 2: Docetaxel: 30 mg/m^2 Cisplatin: 20 mg/m^2 Dose level 3: Docetaxel: 30 mg/m^2 Cisplatin: 25 mg/m^2 Dose level 4: Docetaxel: 30 mg/m^2 Cisplatin: 25 mg/m^2
Administration:	**Phase I:** Dose level 1, 2, 3 & 4: Docetaxel: 30 minutes intravenous infusion weekly for 3 weeks followed by 1 week break (= 1 cycle) Cisplatin: 30 minutes intravenous infusion weekly for 3 weeks followed by 1 week break (= 1 cycle)

Duration of treatment: **Phase I:** Subjects continued treatment till evidence of progression, excessive toxicity necessitating withdrawal from study, or subject desire to withdraw from study.	**Duration of observation:** **Phase I:** Patients were followed every 8 weeks after the end of study date (until death).

Reference therapy: Dose: Administration:	Not applicable
Criteria for evaluation:	
Efficacy:	Not applicable

Safety:	**Phase I:** MDT (Maximum Tolerated doses) defined as the dose at which a DLT (dose limiting toxicity) is experienced during the cycle DLT is defined as any of the following occurring during cycle 1: <u>Hematologic:</u> • absolute granulocyte count < 0.5 x 10^9/L for ≥ 7 days • platelets < 10 x 10^9/L and / or thrombocytopenic bleeding requiring transfusion • febrile neutropenia Non-hematologic: • grade 3 or 4 non-hematologic toxicity (exceptions: alopecia, transient transaminase elevations, unpremedicated nausea / vomiting and unpremedicated hypersensitivity reactions). Adverse events as reported by the subject or noted by the investigator. Standard hematology and blood chemistry.
Pharmacokinetics:	In a previous phase I study of docetaxel and cisplatin delivered every 3 weeks there was no apparent PK interactions between docetaxel and cisplatin. Recommendation for docetaxel followed by cisplatin. Limited PK was performed as this was a new schedule with weekly docetaxel and cisplatin. Determination of drug concentration in plasma: • Docetaxel • Cisplatin
Pharmacokinetic sampling times and bioanalytical methods:	Five-ml samples were collected in heparinized tubes at the following times points: before docetaxel infusion (T=0), 30 min, 45 min, 1, 1.25, 1.5, 2, 4, 7 and 24 h after the initiation of docetaxel infusion. These samples corresponded with the following time points: before cisplatin infusion, 15, 30, 45, 60 min, and 1.5, 3.5, 6.5 and 23.5 after the initiation of cisplatin infusion. Pharmacokinetic samples were collected on the treatment day in week 1 of cycle 1. On the 3rd treatment week of cycle 2 a single blood test following cisplatin infusion was drawn to assess level of docetaxel and cisplatin. The site selected to draw pharmacokinetic samples differed from the infusion site. Bioanalytical method: The site's own local laboratory was used to assess the laboratory parameters listed below. Determination of drug concentrations in plasma **Docetaxe**l: Docetaxel concentrations in plasma were determined using the method described by Vergniol et al. 1992. Paclitaxel was used as the internal standard. 1.0 ml of plasma was subjected to solid-phase extraction performed on Bond Elut C2 columns (100 mg/ml, Varian). The columns were conditioned with 1.0 ml of methanol and 1.5 ml of 0.3% ortho-phosphoric acid. After applying the sample (1.0 ml plasma), the columns were rinsed with 1.0 ml 0.3% ortho-phosphoric acid and washed with 1.0 ml methanol/0.3% ortho-phosphoric acid

	(50/50, v/v). Docetaxel was eluted with 0.3 ml of methanol/0.3% ortho-phosphoric acid (90/10, v/v), and 0.1 ml was injected into an Agilent 1100 HPLC system. The analytical column was a Zorbax Eclipse XDB-C18 (5 µm, 4.6 X 250 mm) preceded by an Eclipse XDB-C18 guard column. The mobile phase was a methanol/0.3% ortho-phosphoric acid (67/33, v/v), delivered at 1.0 ml/min. Docetaxel and the internal standard were detected by an Agilent 1100 diode array detector. **Cisplatin**: Plasma was ultrafiltrated (2000 X g for 30 min) using Amicon centrifree micropartition devices (MW 30,000 cut-off) (Millipore Corporation, Nepean, ON). Cisplatin was analyzed as protein free elemental platinum (Pt) by flameless atomic absorption spectrometry (FAAS). A Varian model AA-220Z/GTA-110 (Varian Inc. Mulgrave, Australia) with Zeeman background correction, equipped with Varian graphite partition tubes and a Varian Pt hollow cathode lamp was used. The ultrafiltrate Pt samples was hot-injected into the graphite furnace at 80 °C in a single volume of 20 µl per sample and the Pt absorbance was read at 265.9 nm.
Statistical methods:	Data were summarized for all safety and intent-to-treat populations using means, standard deviations, medians, maxima and minima for continuous variables and frequencies and percentages for categorical variables. Analysis of safety variables**:** ***Adverse events*** All adverse events, including non-treatment-emergent adverse events, were listed. The proportion of subjects with treatment emergent adverse events (TEAE), overall and by body system, were tabulated for each treatment group. In addition, subjects with possibly related TEAE, serious adverse events, and adverse events leading to withdrawal were listed overall and, if appropriate, frequency distributions by body system were provided. Serious adverse event hypoglycemia was handled in the same way as all other serious adverse events. *Laboratory variables* • Hematology and clinical chemistry o Fisher's exact test (two categories, two treatment groups) was used to compare the treatment groups for the proportion of subjects with PCAs. The mean, median, standard deviation, minimum, and maximum of all laboratory variables were calculated for baseline, each visit, endpoint, and the change from baseline to endpoint. o All clinically noteworthy abnormal laboratory values were listed and commented on by the Medical Advisor.

Summary:

In this study, 16 patients have been enrolled for the phase I, in order to determine the MDT at the first treatment cycle. The phase II portion of this study was not conducted.

From the 16 patients recruited for this study, there were 3 patients in groups 1, 3 and 4 and 7 patients in group 2.

Study completion

Characteristic	Statistic	All subjects	Dose level			
			1	2	3	4
Number of patients	Number	16	3	7	3	3
Withdrawn	Number (%)	5 (31.3)	0 (0)	3 (42.9)	1 (33.3)	1 (33.3)
Duration of study drug (days)	Mean (SD) Median Range	82.8 (46.32) 72 15 - 161	84.0 (62.48) 52 44 - 156	68.4 (39.33) 72 15 - 126	101.0 (51.96) 71 71 - 161	97.0 (57.66) 92 42 - 157
Duration of study (days)	Mean (SD) Median Range	312.9 (130.9) 333 122 - 533	419.3 (100.2) 381 344 - 533	309.4 (151.4) 329 141 - 500	344.3 (40.50) 337 308 - 388	183.0 (65.37) 175 122 - 252
Reason for withdrawal	Number (%)					
Death		1 (6.3)	0 (0)	1 (14.3)	0 (0)	0 (0)
Progressive disease		2 (12.5)	0 (0)	1 (14.3)	0 (0)	1 (33.3)
Did not wish to continue		2 (12.5)	0 (0)	1 (14.3)	1 (33.3)	0 (0)

Demography

Characteristic	Statistic	All subject	Dose level			
			1	2	3	4
Number of patient	Number	16	3	7	3	3
Age (years)	Mean (SD) Median Range	57.9 (10.13) 61 35 - 71	52.7 (10.26) 50 44 - 64	57.1 (12.28) 61 35 - 71	58.3 (9.61) 60 48 - 67	64.3 (3.79) 66 60 - 67
Gender	Number (%)					
Males		13 (81.3)	2 (66.67)	6 (85.7)	2 (66.67)	3 (100.0)
Females		3 (18.8)	1 (33.3)	1 (14.3)	1 (33.3)	0 (0)
Race						
White	Number (%)	13 (81.3)	3 (100.0)	6 (85.7)	2 (66.67)	2 (66.67)
Black	Number (%)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
Asian	Number (%)	2 (12.5)	0 (0.0)	1 (14.3)	1 (33.3)	0 (0.0)

Efficacy results:	Not applicable
Safety results:	All subjects had a treatment emergent adverse event during this study in different organ (nervous system, gastrointestinal system and etc.). 3 patients had an adverse event leading to a permanent discontinuation. These adverse events were classified as grade 3 or 4 toxicity.

Pharmacokinetic results:	

		Docetaxel / cisplatin			
		25 mg / 20 mg	30 mg / 20 mg	30 mg / 25 mg	35 mg / 25mg
Area under curve	Mean	0.824 (0.6435)	1.292 (0.4915)	1.048 (0.1634)	1.376 (0.2970)
	Median	1.02 (0.11- 1.35)	1.14 (0.81- 1.66)	0.98 (0.93- 1.23)	1.32 (1.11- 1.70)
	Range (min - max)	0.11 - 1.35	0.80 - 2.08	0.93 - 1.23	1.11 - 1.70
	Number of subjects	3	7	3	3
Cmax (mcg/L)	Mean	1.213 (0.9677)	2.217 (0.7345)	1.575 (0.0941)	2.300 (0.2636)
	Median	1.39 (0.17- 2.08)	2.01 (1.86- 2.40)	1.52 (1.52- 1.68)	2.29 (2.04- 2.57)
	Range (min - max)	0.17 - 2.08	1.47 - 3.75	1.52 - 1.68	2.04 - 2.57
	Number of subjects	3	7	3	3
Tmax (hr)	Mean	0.52 (0.025)	0.55 (0.052)	0.53 (0.058)	0.51 (0.017)
	Median	0.52 (0.50-0.55)	0.52 (0.52-0.58)	0.50 (0.50-0.60)	0.50 (0.50-0.53)
	Range (min - max)	0.50 - 0.55	0.50 - 0.65	0.50 - 0.60	0.50 - 0.53
	Number of subjects	3	7	3	3

Date of report:	27 December 2007