Comparison of intratumoral docetaxel exposure in cancer patients between nanoparticle entrapped docetaxel (CPC634) and conventional docetaxel (Cd): the CriTax study

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Introduction

Treatment failure of chemotherapy may partly be caused by subtherapeutic intratumoral drug levels.

Nanomedicines are developed to improve the therapeutic index, by increasing intratumoral drug exposure and preserving healthy tissues.

CPC634 is a nanomedicine consisting of docetaxel entrapped in 65 nm sized polymeric micelles.

Preclinical data demonstrated that after CPC634 infusion higher intratumoral docetaxel concentration were reached compared to conventional docetaxel (Cd).[1]

We hypothesized that CPC634 increases intratumoral docetaxel level and overall exposure in a clinical setting.

Objectives

The primary objective was to demonstrate a 25% increase in intratumoral docetaxel concentration of CPC634 compared to Cd.

Secondary objectives were to compare the systemic pharmacokinetic profile of CPC634 with Cd and to evaluate the safety profile of CPC634 and compare this with Cd.

Methods

Randomized cross-over pharmacokinetic study (NCT02442531).

Patients with solid tumors without standard treatment options were included.

Both plasma and intratumoral pharmacokinetics (PK) of docetaxel after intravenous administration of 75 mg/m^2 Cd and CPC634 were assessed.

A single tumor biopsies were taken at 24, 48, 72, 96, 168 and 360 hours after administration of CPC634 and Cd. Four patients were included per timepoint.

Total docetaxel (TDC) was determined for both drugs and released docetaxel for CPC634 in tumor tissue and in plasma using a validated LC-MS/MS method.[2]

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CONCLUSION

CPC634 revealed a prolonged higher systemic and intratumoral docetaxel exposure compared to conventional docetaxel.

Table 1. Patients characteristics.

Characteristics	n = 33
Age	
Median (IQR)	64 (16.5)
Gender	
Female	9 (27.3%)
Male	24 (72.7%)
WHO	
0	9 (27.3%)
1	24 (72.7%)
Randomization	
Arm A	16 (48.5%)
Arm B	17 (51.5%)

Table 2. Relative difference (RD) in plasma and intratumoral PK.

Plasma pharmacokinetics	RD	95% CI	P value
Released docetaxel vs conventional docetaxel			
AUC_{inf}	27.05	11.96 to 44.18	0.001
C_{max}	-90.95	-92.04 to -89.70	<0.001
Total docetaxel vs conventional docetaxel			
AUC_{inf}	26474	23076 to 30369	<0.001
C_{max}	1438	1282 to 1612	<0.001
Intratumoral concentration	**RD**	**95% CI**	**P value**
Released docetaxel vs Cd	17.3	-22.26 to 76.99	0.43
Total docetaxel vs Cd	460.57	243.19 to 815.65	<0.001

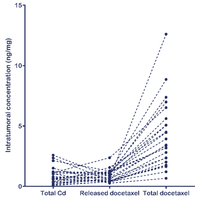


Figure 1. Intratumoral concentrations per patient.

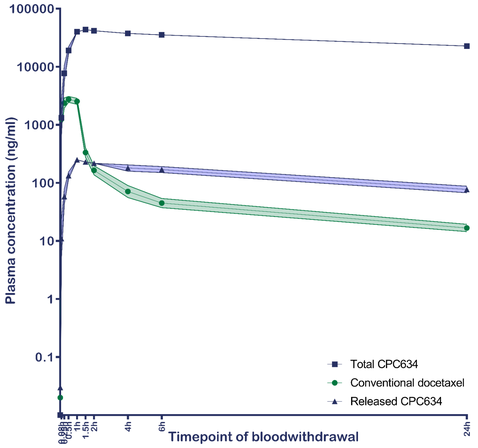


Figure 2. AUC_{0-24h}. Shading represents 95% confidence interval.

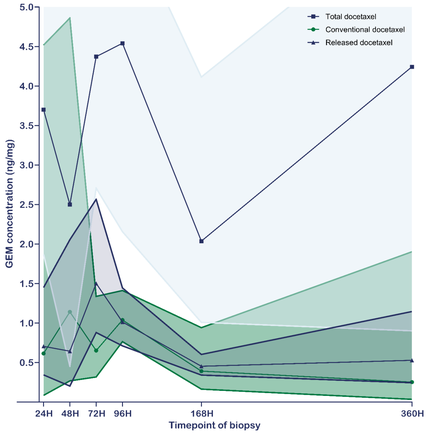
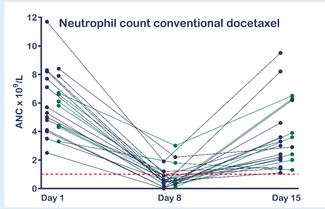


Figure 3. Geometric mean (GEM) intratumoral concentrations per timepoint. Shading represents 95% confidence interval.

Results

Adverse events	Conventional docetaxel		CPC634	
	Grade 1-2 (%)	Grade ≥3 (%)	Grade 1-2 (%)	Grade ≥3 (%)
Nausea	9(30)	1 (3.3)	11 (37.9)	2 (6.9)
Vomiting	2 (6.7)	1 (3.3)	6 (20.6)	1 (3.4)
Anorexia	14 (46.6)	1 (3.3)	11 (37.9)	1 (3.4)
Stomatitis	9 (30)	1 (3.3)	10 (34.5)	2 (6.9)
Constipation	7 (23.3)	1 (3.3)	6 (20.7)	0
Diarrhea	9 (30)	1 (3.3)	8 (27.8)	1 (3.4)
Abdominal pain	2 (6.6)	1 (3.3)	5 (17.2)	0
Pain	7 (23.3)	5 (16.7)	15 (51.7)	1 (3.4)
Rash	12 (40)	0	19 (65.5)	0
Hand-footskinreaction	2 (6.6)	1 (3.3)	3 (10.9)	0
Fatigue	16 (53.4)	3 (10)	10 (34.4)	4 (13.8)
Edema	4 (13.4)	0	2 (6.8)	0
Dyspneu	7 (23.3)	0	4 (13.7)	1 (3.4)
Cough	2 (6.7)	1 (3.3)	2 (6.9)	0
Alopecia	11 (36.6)	0	7 (24.1)	0
Dizziness	3 (10)	0	6 (20.7)	0
Ototoxicity	1 (3.3)	0	2 (6.9)	1 (3.4)
Sensible neuropathy	1 (3.3)	1 (3.3)	6 (20.7)	0
Chills	1 (3.3)	0	3 (10.3)	0
Infection	1 (3.3)	6 (20)	2 (6.9)	1 (3.4)
Fever	4 (13.3)	0	2 (6.9)	0
Neutropenic fever	0	3 (10)	0	0
Sepsis	0	1 (3.3)	0	0
Creatinine	8 (28)	0	9 (30)	0
Albumin	9 (31)	0	4 (13)	0
AST	5 (17)	0	11 (37)	1 (3)
ALT	3 (10)	0	5 (17)	0
GGT	5 (17)	3 (10)	1 (3)	5 (17)
AP	4 (14)	2 (7)	1 (3)	2 (7)
Bilirubin	0	0	2 (6)	0
Hb	4 (14)	0	6 (20)	0
Platelets	6 (21)	0	7 (23)	0
ANC	6 (21)	20 (70)	9 (30)	1 (3)

Table 3. Treatment emergent adverse events (TEAEs) occurring in ≥ 3 patients during treatment with Cd or CPC634.



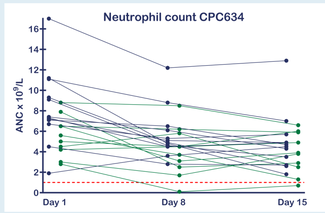


Figure 4. Neutrophil count after administration of Cd or CPC634. Green represents first cycle.

Discussion

Higher (RD = 460%) intratumoral total docetaxel levels were reached with CPC634, while released docetaxel levels were comparable to conventional docetaxel (RD = 17.3%).

The plasma PK profile of CPC634 is characterized by a lower C_{max} (-91%), lower clearance (-15%) and prolonged higher systemic exposure compared to conventional docetaxel.

CPC634 resulted in a lower incidence of neutropenia most likely due to the lower C_{max} values.

Data regarding a phase 1 study with CPC634 was presented at ASCO 2019.[3] Additional studies assessing the intratumoral exposure to CPC634 (NCT0371243) and a phase II efficacy study of CPC634 in platinum resistant ovarian cancer patients (NCT03742713) are currently ongoing.

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