Metabolic Activation and Inactivation of Irinotecan when Combined with the Human Monoclonal Antibody Bevacizumab

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Abstract: *Purpose*: This pharmacokinetic study was designed to investigate whether the co-administration of the monoclonal antibody bevacizumab (BVC) shows potential to modulate the plasma disposition of irinotecan (CPT-11) and its metabolites.

Patients and Methods: Ten patients suffering from advanced colorectal cancer entered this pharmacokinetic study. Patients received CPT-11 as a 60 min i.v. - infusion (180 mg/m2, total dose 339 ± 32 mg) weekly for six weeks. BVC was administered biweekly as an intravenous 90 min infusion containing 5 mg BVC per kg body weight in 100 ml balanced sodium chloride solution. Pre-medication consisted of tropisetrone (3 mg i.v. push) and atropine (0.5 mg i.v.) one hour before CPT-11 infusion. Plasma samples were analysed during / after the first (MONO) and after the third CPT-11 infusion (BVC regimen).

Results: BVC did not alter plasma disposition and pharmacokinetics of the parent compound CPT-11, but in contrary BVC appeared to lower the plasma concentrations of the metabolites SN-38, SN-38gluc and APC.

Conclusion: Overall, our findings indicate that administration of BVC prior to chemotherapy showed no clinically significant impact on the pharmacokinetics and metabolic activation of CPT-11.

Keyword: CPT-11, metabolites, pharmacokinetics, bevacizumab, advanced colorectal cancer, enzymatic activation.

INTRODUCTION

The topoisomerase-I inhibitor irinotecan (CPT-11), a camptothecin derivative, is highly active as a single agent or when combined with 5-fluorouracil (5-FU) + leucovorin for patients with advanced colorectal cancer (CRC). As first-line therapy, the combination of CPT-11 and 5-FU/LV significantly improves response rate, time to disease progression and over-all survival compared with 5-FU/LV alone [1,2]. CPT-11 itself represents a prodrug that undergoes excessive biotransformation in man by different metabolic routes. CPT-11 is needs to be activated into the pharmacologic active metabolite SN-38 by the human carboxyesterase isoenzyme II (hCE2) and *via* another biotransformation route into the pharmacological inactive metabolite APC by CYP3A4. Further SN-38 is detoxified by UGT1A1 into SN-38-ß-D-glucuronide. All metabolic pathways are sensitive for drug-drug interactions.

Bevacizumab (BVC) is a recombinant, humanized, monoclonal antibody designed to specifically inhibit vascular endothelial growth factor, a protein that plays a major role in angiogenesis and the maintenance of existing blood vessels of multiple malignant tumours.

A single dose of bevacizumab 0.1–10 mg/kg yields a plasma peak concentration of 2.8 – 284 µg/ml and shows a dose–response relationship [3]. Pre-clinical and clinical studies have shown that BVC has both cytostatic and cytotoxic effects, resulting in a reduction in tumor growth and increases in median survival time and time to tumor progression.

BVC is available as an intravenous agent and carries FDA-approved labelling for use in the first-line treatment of metastatic colorectal cancer in combination with fluorouracil-based chemotherapy (Saltz regimen). BVC 5 mg/kg is infused intravenously over 30–90 minutes every two weeks. No dosage reduction is required for patients with renal or hepatic dysfunction.

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BVC has been combined with various antineoplastic agents (paclitaxel, capecitabine, gemcitabine, carboplatin and others) with no clinical issues [4]. In one clinical trial concerning the combination of BVC with CPT-11 for treatment of metastatic colorectal cancer, altered plasma concentrations of SN-38 have been reported in the combination regimen [5, 6]. The combination of CPT-11 and BVC has been also introduced as first line therapy [7,8]. It should be noted that BVC inhibits the biological activities of vascular endothelial growth factor (VEGF), and so the blood and / or tissue transfer of another drug could be modulated.

The purpose of this investigation was to determine to what extent BVC influences the plasma disposition of CPT-11 and its metabolites when CPT-11 is co-administered with BVC to ACRC patients who were already on CPT-11 infusion for two weeks.

CLINICAL STUDY

Study Subjects

Ten patients (2 female, 8 male) who received CPT-11 plus BVC for advanced CRC entered the pharmacokinetic study. Written informed consent was obtained from each patient according the specifications of the ethics committee of the University of Vienna. Inclusion criteria were as follows: Karnofsky index > 70%; white blood cell count > 4000/µl; WHO performance status of 1; no renal impairment as judged by standard biochemical parameters (plasma creatinine < 1.5 mg/dl); and no hepatic impairment (bilirubin < 0.6 mg/dl, γ-glutamyl-transferase < 100 U/l and alanine-aminotransferase < 30 U/l).

Mean (± SD) age was 68 ± 6 years (range 33 – 72 years), mean body mass was 78 ± 12 kg (range 66 – 93 kg), mean height was 174 ± 7 cm (range 167 – 182 cm) and mean body surface area was 1.92 m^2 (range 1.77 –2.13 m^2).

Study Design and Treatment

The study had prospective crossover design with patients serving as their own controls so as to reduce problems associated with inter-patient variability. CPT-11 (Campto®) was supplied as a sterile solution containing 40 mg in 2 ml vials (Pfizer, Vienna, Austria).

Patients received CPT-11 (FOLFIRI) through a central venous infusion for 60 min biweekly (180 mg/m^2, mean total dose 339 ±32 mg, mean infusion rate 5.65 mg/min). Thereafter Leucovorin 200 mg/m2 over 2 h was administered followed by a 5FU bolus 400 mg/m2 and a 5FU continuous 46 –h infusion (2400 mg/m2).

BVC (Avastin®, Hoffmann La Roche, Austria) was given biweekly as an intravenous infusion containing 5 mg BVC per kg BW in 100 ml isotonic sodium chloride solution. Infusion time was 60 min. The first BVC infusion was given on day 1 immediately after CPT-11 infusion. By this procedure the first cycle was the MONO arm and the third cycle the combination arm with BVC.

Sample Collection

Whole blood samples of 4.0 ml were drawn from the cubital vein during the first cycle (day 1, MONO) and third cycle of therapy (day 15, BVC) at the following times: 1 hour prior to infusion and 45, 60, 70, 90, 105, 120, 180 and 240 min after start of infusion. After centrifugation at 2500 rpm for 5 minutes to remove blood cells, 2 ml of the plasma was stored at – 80°C until analysis. Sample clean-up and analysis had to be performed within two weeks to avoid further formation of SN-38 from CPT-11 due to activity of hCES even when frozen.

Sample Clean-Up

One ml of plasma sample was mixed with 3.0 ml of a mixture of ice-cold acetonitrile / methanol (1:1, v / v %) and vortexed for 2 min. After protein precipitation had completed the sample was centrifuged in a cool centrifuge for 3 min at 10 000 rpm (4 ^oC). From the supernatant, an aliquot of 1000 µl was acidified with 20 µl of phosphoric acid (8.5 %) to shift the equilibrium from the carboxylate to the lactone form, vortexed for 1 min and was put into the autosampler micro vial.

Chromatography

Total amounts of CPT-11, SN-38, SN-38gluc and APC were quantified in plasma samples by isocratic reversed-phase HPLC using fluorimetric detection as described previously [9, 10].

Biometric Calculations

Pharmacokinetic calculations were carried out by use of commercially available computer software (Kinetica, version 5.1; Waltham, MA 02454). Following PK meters were estimated:

t_{max} = time of peak plasma concentration [h]

c_{max} = peak plasma concentration [µg/ml CPT-11]

c_{max} = ng/ml for metabolites

AUC_{0-4} = area under the concentration-time curve from 0 to 4 hours [µg/ml*h]

V_{dss} = volume of distribution at steady state [l]

Cl_{tot} = total body clearance [l/h]

MRT = mean residence time [h]

The following pharmacokinetic parameters were calculated for SN-38 using the software "PKSolutions" version 1.1 (Summit Inc., USA).

$k_{app}in$ = apparent half-life of formation [h^{-1}]

t_{max} = time of peak plasma concentration [h]

c_{max} = peak plasma concentration [ng/ml]

AUC_{0-4} = area under the plasma-concentration-time curve from 0 to 4 h [µg/ml*h]

MRT = mean residence time [h]

Statistical calculations including Student'S paired t-test and descriptive statistics were carried out through Microsoft® Excel™ 2010-Data Analysis Tool, Microsoft Corporation.

An apparent activity of enzyme [R] for hCE has been calculated by dividing the formed metabolite AUC_{0-4} by its precursors AUC_{0-4}

$$R_{hce} = AUC_{SN38}/AUC_{CPT11}$$

RESULTS

As depicted in Figure **1**, mean plasma concentration-time curves for CPT-11 declined similar in the CPT-11 MONO and BVC arm of the study. Mean peak concentrations (see Table **1** which summarizes the pharmacokinetic parameters of CPT-11 and SN-38.) occurred close to the end of infusion after MONO (0.9 h) and BVC (0.85 h), respectively.

Interestingly in both arms of the study in some patients a weak "rebound effect" (redistribution from tissue or from gut into the blood) of CPT-11 plasma concentrations had been observed between 75 and 120 minutes. Overall, the plasma concentrations of CPT-11 were insignificantly lower after BVC regime.

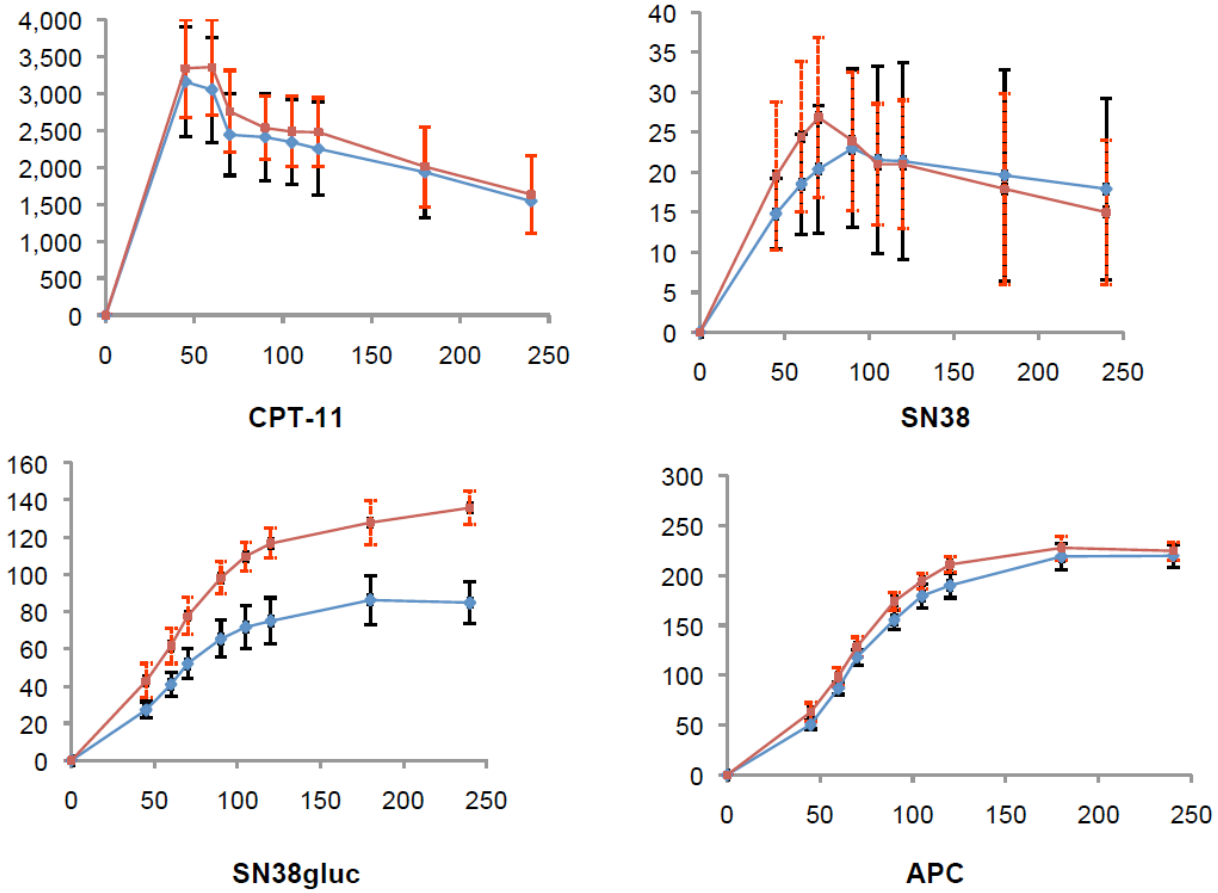

Figure 1: Mean plasma concentration time curves of CPT-11, SN-38, SN-38gluc and APC in patients receiving CPT-11 during the MONO therapy and when combined with BVC.

Table 1: Summary of PK Parameters for CPT-11 and its Metabolite SN38 Alone and in Combination with BVC

Parameter	Unit	MONO Mean±SD	+ BVC Mean±SD
SN38			
C_{max}	µg/L	29.89±11.86	26.00±11.21
T_{max}	h	1.34±0.61	2.18±1.04
AUC_{last}	µg/L*h	72.03±25.03	69.83±33.50
MRT	h	4.91±1.62	5.41±1.84
k_{in}	min-1	0.043±0.053	0.021±0013
CPT11			
C_{max}	µg/L	3530±638	3341±653
T_{max}	h	0.90±0.12	0.85±0.12
AUC_{last}	µg/L*h	8764±1688	8201±2009
MRT	h	6.49±3.84	6.80±3.74
Clearance	L/h	11.50±4.89	12.11±5.73
V_d	L	58.46±11.71	65.67±17.71
$k_{appformation}$	min-1	0.216±0.101	0.196±0.078

Lasma concentrations of the metabolite SN-38 were much lower and reached its peak concentration within 70 - 105 min after start of CPT-11 infusion. BVC showed a weak effect on the disposition of SN-38: peak concentration (c_{max} = 26.89 ng/ml at 70 minutes for the MONO and 23.00 ng/ml at 90 minutes for the BVC regimen). Mean plasma concentrations were found lower in BVC combined regimen. However, due to the inter-patient variability this observation was statistically insignificant.

In both the treatments the phase-II conjugate of SN-38, the corresponding ß-D-glucuronide SN-38gluc, was detectable in our first samples at 45 minutes after starting the infusion. Up to our last sample at 240 minutes the plasma concentration was in ascending phase and peak was certainly beyond 4 hrs whereas in the BVC treatment mean peak was found to be 86 ng/ml at 180 minutes much later than that of SN-38 which were found to be between 70 - 105 min. SN-38gluc eliminates *via* the faecal route, so the observed plasma concentrations represent only the portion that had been redistributed from bile into the blood. In the presence of BVC, SN-38gluc plasma concentrations were significantly lower; see Figure **1**.

CPT-11 pharmacokinetics remained unaffected in combined BVC treatment. Descriptive Statistics of PK parameters for CPT-11 in Control and Combination therapy along with Paired T-Statistics are reported in Table **2**. In the two treatments all the parameters C_{max}, T_{max}, AUC_{last}, MRT, Clearance, V_d and k_{in} were found insignificantly different at 0.05 level of significance. Statistically insignificant but visually evident a small decrease in peak plasma concentration can be seen in Figure **1**.

Table **3** reports descriptive statistics of PK parameters for SN38 in both the treatments along with Paired T-Statistics. Here it can seen that a significant (at 0.05 level of significance) earlier and higher maximum concentration in combination therapy; if it does not surpass the maximum tolerable toxicity certainly combination is of more and early therapeutically effective.

In consequence of earlier and higher peak concentration the area under the concentration-time curve upto last sampling (AUClast) is also greater at 0.06 level of significance.

In Combination versus Control the formation half lives were found to be 31.16±19.74 vs 50.74±37.31 minutes thus the higher Cmax, Tmax and AUClast are supported by shorter formation half life (accelerated rate of formation), although it is not as highly significant as these parameters (at 0.05 level) but at 0.1 level which is also considerable particularly when we found that due to this higher formation consequently significant different PK parameters are established. Detailed elucidation of this inference should be verified on larger sample size.

Table 2: Pk Metrics for CPT-11 in Control and Combination Therapy for All Patients along with Paired T-Statistics

	Cmax	Tmax	AUClast	MRT	Clearance	Vd	Kin
Combination	2532	1.00	5791	5.14	16.63	85.44	0.122
	3116	1.00	8140	3.34	15.66	52.31	0.055
	4299	1.00	10557	8.99	6.06	54.44	0.224
	3266	0.75	9679	15.15	4.06	61.58	0.418
	2870	1.00	6810	4.34	15.86	68.81	0.131
	2979	0.75	7015	3.41	17.93	61.12	0.266
	3867	0.75	10073	4.58	10.25	46.96	0.262
	3662	1.00	8601	4.36	12.55	54.70	0.194
	4465	1.00	11052	11.58	4.59	53.11	0.216
	4244	0.75	9933	4.03	11.45	46.10	0.275
Control	2035	0.75	4764	5.35	19.87	106.24	0.249
	2733	0.75	6271	3.72	19.07	70.91	0.282
	3951	0.75	9628	7.86	7.30	57.40	0.214
	3549	0.75	9171	12.51	5.27	65.92	0.259
	3092	1.00	5834	3.79	20.28	76.92	0.136
	3608	1.00	9237	3.62	13.13	47.54	0.102
	3648	0.75	8506	5.34	11.09	59.26	0.267
	4385	0.75	11077	5.01	8.84	44.26	0.249
	3668	1.00	10524	15.08	3.73	56.27	0.119
	2748	1.00	7005	5.73	12.57	71.99	0.079
Combination Mean	3530	0.90	8765	6.49	11.50	58.46	0.216
Standard Deviation	674	0.13	1779	4.05	5.16	11.71	0.101
Control Mean	3342	0.85	8202	6.80	12.11	65.67	0.196
Standard Deviation	689	0.13	2118	3.94	6.04	17.71	0.078
Difference Mean	188	0.05	563	-0.31	-0.61	-7.22	0.021
Standard Error	214	0.06	536	0.52	0.95	4.05	0.043
t-Statistics	1	0.80	1	-0.60	-0.65	-1.78	0.484
P-Value	0.4 (ns)	0.44 (ns)	0.32 (ns)	0.56 (ns)	0.53 (ns)	0.11 (ns)	0.64 (ns)

ns= not significantly different; * significantly different.

Table 3: PK Metrics for SN38 in Control and Combination Therapy for All Patients along with Paired T-Statistics

	C_{max}	T_{max}	AUC_{last}	MRT	$k_{appformation}$	$T_{1/2\ form}$
Combination	8	1.00	24.38	7.50	0.032	21.6
	29	1.17	71.78	5.00	0.018	39.2
	15	1.17	46.99		0.055	12.6
	48	3.00	119.31		0.004	184.8
	37	1.17	72.88	4.46	0.046	15.1
	38	1.50	88.70	2.87	0.012	57.2
	31	1.17	70.30	3.25	0.013	53.4
	24	1.17	67.58	6.96	0.044	15.6
					0.016	43.3
	39	0.75	86.30	4.35	0.186	3.7

(Table 3). Continued.

	C_{max}	T_{max}	AUC_{last}	MRT	$k_{appformation}$	$T_{1/2\ form}$
Control	7	1.50	19.13	5.42	0.0200	34.7
	18	1.17	43.90	3.77	0.0425	16.3
	16	4.00	43.45			
	31	4.00	88.50			
	21	1.17	46.78	3.87	0.0374	18.5
	36	2.00	92.13	5.06	0.0075	92.0
	26	1.50	67.90	3.68	0.0115	60.4
	28	1.50	77.65	7.11	0.0227	30.6
	50	3.00	146.23		0.0058	119.8
	27	2.00	72.58	8.95	0.0206	33.6
Combination Mean	29.89	1.34	72.03	4.91	0.0425	31.16
Standard Deviation	12.57	0.65	26.55	1.75	0.0531	19.74
Control Mean	23.33	2.09	61.34	5.41	0.0210	50.74
Standard Deviation	8.77	1.12	24.34	1.98	0.0133	37.31
Difference Mean	5.90	-0.67	9.62	-0.35	0.0257	-19.58
Standard Error	2.38	0.27	4.51	0.59	0.0167	10.23
t-Stats	2.48	-2.46	2.13	-0.59	1.5419	-1.91
P-Value	0.03 (*)	0.03 (*)	0.06 (ns)	0.57 (ns)	0.15 (ns)	0.09 (ns)

ns= not significantly different; * significantly different.

The formation of SN-38 seemed to be delayed when BVC had been pre-administered. Apparent formation rate decreased (t1/2 = 31.16±19.74 min instead of 50.74±37.31 min) leading to a slightly lower peak concentrations (23.33±8.77ng compared to 29.89±12.57ng) the combination regimen.

Apparent activity of hCE has been calculated by dividing the AUC_{0-4} of formed metabolite/drug by its precursors AUC_{0-4}

R_{hce} in Mono Therapy =61.34/8201=0.0075

R_{hce} in BVC Therapy =72.03/8765=0.00822

DISCUSSION

The aim of this pharmacokinetic study was to determine the plasma disposition of CPT-11 and its main metabolites in patients receiving chemotherapy with weekly CPT-11 alone and plus BVC from third weeks.

While we did not set out to evaluate anti-tumor response, efficacy data were collected in this group of patients. Dose reduction of CPT-11 was not necessary, because no grade 3/4 adverse events (haematological events or hand-foot syndrome) could be observed.

Any change of formation rate and plasma disposition, especially of SN-38, is of essential clinical importance because the compound is highly toxic and only small amounts of this pharmacologic active metabolite can be measured in blood (below 100 ng/ml).

CPT-11 undergoes rapid inter-conversion from the lactone into its carboxylate form in the presence of protein. The equilibrium of lactone – carboxylate forms of CPT-11 and its active metabolite SN-38 depends on the pH of the solution: pH values higher than 7.0 tend to result in the carboxylate form. To obtain total amount of lactone we shifted the equilibrium to the site of lactone by acidifying the plasma samples. In this way it was possible to measure the total concentrations / amounts of all analytes as recommended [11].

The pharmacokinetic profile of CPT-11 is rather complex as a result of the multiple biotransformation pathways involving various enzymes (hCE, CYP3A4, UGT1A1). As a carbamate, CPT-11 is a relatively poor substrate for hCE [12]. This is thought to be the result of slow decarbamylation of the serine esteratic site of hCE, inferring that CPT-11 is a slowly competitive inhibitor. Assuming that there is some type of pharmacokinetic interaction, it is possible that CPT-11

could be inhibited by xenobiotic high turnover substrates of hCE, which is rapidly metabolised by hCE [12, 13]. Generally, the low affinity of CPT-11 for hCE only generates small amounts of the active compound SN-38 lactone in the body (30–100 pmol). Nevertheless, because of the high anti-tumour activity of SN-38 (approximately 100 – 1000 times that of CPT-11) these concentrations are sufficient for an effective anticancer therapy.

Recent data showed that a pharmacokinetic (PK) drug interaction may occur between CPT-11 and some other antineoplastic drugs as carboplatin [14], paclitaxel [15] and 5-fluorouracil [16]. Co-administered drugs that are metabolised by the same enzymes (hCE, CYP3A4, UGT) may influence the metabolism of CPT-11.

In the present work R_{hce} in Combination (BVC) Therapy was found be 0.00822, a little higher than for mono therapy which was found to be: 0.0075

CONCLUSION

Metabolism of CPT-11 is rather complex and plasma disposition of metabolites not only depends on their formation rate but also on their blood to tissue transfer or liver blood flow as well as enterohepatic circulation as has already been discussed for SN-38gluc. Another reason for altered plasma disposition of CPT-11 metabolites:

Since VEGF regulates vascular proliferation and permeability, vascular dysfunction is an area of concern with angiogenesis inhibitors (e.g. bleeding or thrombotic events) [17, 18]. In the presence of high levels of VEGF (that occur in cancer), vasculature becomes excessively permeable and leaky. This leads to an uneven delivery of nutrients, oxygen and therapeutic agent to the tumour.

A vascular dysfunction as leaky membranes or endothelium may lead to altered distribution of CPT-11 and metabolites from blood into tissue to a certain extent.

Although some small changes of metabolite disposition in the BVC regimen could be observed there was no interaction between CPT-11 and BVC from the pharmacokinetic point of view.

Data of CPT-11 pharmacokinetics plus FOLFIRI combined with or without BVC have been published recently for second line chemotherapy. These finding showed similar results in compare to our investigation with the exception of higher plasma peak concentration, because in that schedule CPT-11 dose was 150 mg/m^2 over 90 min (in our schedule the dose was 180 mg/m^2 over 60 min) [19]. Moreover differences in patients (Caucasians versus Japanese) could be the reason for the observation. Tmax was delayed for SN38 and SN38gluc and AUC_{total} was decreased when BVC was included into the schedule.

Another pharmacokinetic study has been published when CPT-11 plus BVC was given in solid tumours (180 mg/m^2 over 90 min) [3]: c_{max} of SN38 (- 21 %), SN38gluc (- 26%) and APC (-37 %) were clearly decreased in the presence of BVC. In our study decrease was in similar order of magnitude: -23 %, -16% and – 45 %, respectively. Obviously coadministration of BVC leads to lower plasma concentrations of the CPT-11 metabolites.

Interestingly, plasma disposition of CPT-11 metabolites was modulated in a similar order of magnitude when cetuximab was included into the chemotherapeutic schedule. We performed two investigations with weekly and biweekly cetuximab combined with CPT-11 / FOLFIRI with the following results [20, 21]:

Weekly: with cetuximab cmax of SN38 – 24%, of SN38gluc –25 % and of APC -12 %. In the biweekly schedule we found an increase of cmax for SN38 + 14 %, and a decrease of cmax for SN38gluc – 37 % and for APC – 42 %.

Summarizing these observations from different pharmacokinetic studies we conclude that BVC has a certain effect on the plasma disposition of CPT-11 metabolites. In all investigations plasma concentrations of metabolites were lowered at about – 20 % compared to the schedule without monoclonal antibody. These results are remarkable because in all studies the mono and combination regimen was administered to the same patient in a cross over design: pharmacokinetic analysis of CPT-11 and metabolites in the first cycle, followed by BVC for two weeks and repeated pharmacokinetics of CPT-11 in the next cycle.

All authors found no clinical relevancy for the observed decrease of metabolites plasma concentrations due to the high variability of the data sets.

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