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REVIEW ARTICLE

Population pharmacokinetics of FOLFIRINOX: a review of studies and parameters

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Abstract

Purpose FOLFIRINOX regimen is commonly used in colorectal and more recently pancreatic cancer. However, FOLFIRINOX induces significant and dose-limiting toxic effects leading to empirical dose reduction and sometimes treatment discontinuation. Model-based FOLFIRINOX regimen optimization might help improving patients' outcome. As a first step, the current review aims at bringing together all published population pharmacokinetics models for FOLFIRINOX anticancer drugs.

Methods A literature search was conducted in the PubMed database from inception to February 2018, using the following terms: population pharmacokinetic(s), irinotecan, oxaliplatin, fluorouracil, FOLFIRI, FOLFOX, FOLFIRINOX. Only articles displaying nonlinear mixed effect models were included. Study description, pharmacokinetic parameter values and influential covariates are reported. For each model, the typical pharmacokinetic profile was simulated for the standard FOLFIRINOX protocol.

Results The FOLFIRINOX compounds have been studied only separately so far. A total of six articles were retained for 5-fluorouracil, 6 for oxaliplatin and 5 for irinotecan (also including metabolites). Either one- or two-compartment models have been described for 5-fluorouracil, while two- or three-compartment models were reported for oxaliplatin and irinotecan pharmacokinetics. Non-linear elimination was sometimes reported for 5-fluorouracil. Sex and body size were found as influential covariates for all molecules in some publications. Despite some differences in model structures and parameter values, the simulated profiles and subsequent exposure were consistent between studies.

Conclusions The current review allows for a global understanding of FOLFIRINOX pharmacokinetics, and will provide a basis for further development of pharmacokinetics–pharmacodynamics–toxicity models for model-driven FOLFIRINOX protocol optimization to reach the best benefit-to-risk ratio.

Keywords FOLFIRINOX · 5-Fluorouracil · Irinotecan · Oxaliplatin · Population pharmacokinetics · Nonlinear mixed effect modelling

Introduction

FOLFIRINOX regimen is a combination of 5-fluorouracil (5FU) modulated by folinic acid (FA), oxaliplatin and irinotecan (CPT-11). The standard protocol consists of a 2 h infusion of oxaliplatin 85 mg/m^2 with FA 200 mg/m^2 followed by a 90 min infusion of CPT-11 180 mg/m^2, and a 10 min bolus intravenous administration of 5FU 400 mg/m^2 followed by a 46 h infusion of 5FU 2400 mg/m^2, which is repeated every 2 weeks.

5FU is a key cytotoxic agent in the treatment of metastatic colorectal cancer, present in many chemotherapy regimens. 5FU is an anti-metabolite agent that acts on thymidylate synthase (TS) inhibition via the formation of a ternary complex:

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fluorodeoxyuridine monophosphate (FdUMP), TS and 5,10-methylene tetrahydrofolate (5,10-MTHF). FA potentiates the activity of 5FU by stabilizing the complex via the augmentation of the 5,10-MTHF concentration. Inhibition of TS prevents the formation of thymidine and consequently DNA synthesis. 5FU acts specifically on the S phase of cell cycle. 5FU also acts on RNA by incorporating 5FU in place of uracil, which leads to errors in protein synthesis [1]. 80% of administered 5FU is catabolized by dihydropyrimidine dehydrogenase (DPD) before being eliminated in urine. Therefore, patients with a lack of DPD activity are risking severe toxicities due to high concentrations of active 5FU [2]. Although several tools to identify DPD-deficient patients have been developed, few tests are carried out in practice so far. In the standard FOLFIRINOX regimen, 5FU is administered in bolus dose of 400 mg/m^2 followed by a continuous infusion of 2400 mg/m^2 over 46 h. The half-life of 5FU is very short, from 8 to 14 min. 5FU pharmacokinetics (PK) is non-linear due to saturable hepatic degradation [3].

Oxaliplatin is an alkylating chemotherapy drug used as single agent or in combination in the treatment of various types of cancer (colorectal, ovarian, breast, prostate, lung cancer,etc.). Its mechanism of action involves induction of apoptosis of cancer cells through various DNA damages: DNA lesions, arrest of DNA synthesis and inhibition of messenger RNA synthesis [4]. In blood and plasma, oxaliplatin binds in an irreversible manner to different constituents such as erythrocytes and plasma proteins, making it mandatory to distinguish between free and bound platinum for PK studies. Indeed, the unbound fraction, composed of unbound drug and metabolism products, is active and exerts antitumor and toxic actions while the bound fraction is inactive. Therefore, the ultrafilterable platinum (equivalent to unbound fraction) is the most useful part to study in PK [5]. To the best of our knowledge, no tool is currently available to predict oxaliplatin toxicity in routine practice.

CPT-11 is a semisynthetic derivative of camptothecin used primarily in colorectal cancer. CPT-11 is a prodrug which is converted into SN38 (7-Ethyl-10-hydroxy-camptothecin, active form) by carboxylesterase in the liver, and into two inactive forms, APC (7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin) and NPC (7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin), by CYP3A4/5 [6]. SN38 inhibits topoisomerase I and causes double-strand DNA breakage and cell death. SN38 is detoxified by UGT1A1 into SN38G (glucuronidated SN38), an inactive metabolite, before biliary excretion. UGT1A1 activity is highly variable between individuals, which can be due to gene polymorphisms that impact the SN38 PK [7] and subsequently irinotecan efficiency and toxicity. As a consequence, UGT1A1 genotyping is recommended to prevent irinotecan toxicity. SN38 is bound to plasma proteins at 95%. The terminal half-time of CPT-11 ranges from 5 to 27 h and SN38 half-time is between 6 and 30 h. The clearance of CPT-11 is decreased for patients with high bilirubin [8].

The FOLFIRINOX tritherapy was first developed for treatment of colorectal cancer [9]. A phase III clinical trial comparing FOLFOXIRI (combination of 5FU, leucovorin, CPT-11 and oxaliplatin administered with a protocol slightly different from FOLFIRINOX) and FOLFIRI (protocol combining 5FU, leucovorin and CPT-11 only) in metastatic colorectal cancer showed that FOLFOXIRI regimen induced a better therapeutic response [10]. In pancreatic cancer, a phase II study evaluated FOLFIRINOX regimen in single arm and found promising results [11]. Thereafter, the phase II/III PRODIGE 4/ACCORD 11 was conducted to compare FOLFIRINOX to the standard treatment in pancreatic cancer which was gemcitabine, in adult patients with metastatic pancreatic adenocarcinoma, a good Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) scale of performance status (PS) of 0 or 1, and aged 75 years or less [12]. Overall survival was 11.1 months in FOLFIRINOX arm versus 6.8 months for gemcitabine arm. Progression-free survival was 6.4 versus 3.3 months, and response rate 11.1% vs 9.4%. Based on this study, the standard first-line treatment of metastatic pancreatic cancer is currently FOLFIRINOX for patients under 75 years of age, normal bilirubin level and PS 0 or 1. Several phase II studies and off-trial series confirmed these results [13]. Encouraging results about neo-adjuvant FOLFIRINOX in pancreatic cancer patients were first reported in 2015 in a study with 31 patients. The complete resection was performed for 13 patients, allowing a global survival median of 36 months for resected patients [14]. Moreover, in a recent phase III trial, PRODIGE 24, Conroy et al. reported that mFOLFIRINOX (standard regimen modified by irinotecan dose reduction to 150 mg/m^2) was more efficient than gemcitabine as adjuvant treatment in patients with resected pancreatic ductal adenocarcinomas [15]. Guion-Dusserre et al. [16] also recently showed that FOLFIRINOX regimen could be efficient in elderly colorectal and pancreatic cancer patients.

However, to date, the administration protocol relies mainly on an empirical basis, and induces frequent dose-limiting toxicities, leading to an impaired outcome for the patients [17]. Recent studies have in pancreatic cancer patients have shown high rates of severe toxicities, among which dose-limiting grade 3–4 neutropenia and digestive toxicities [18], leading to frequent empirical individual dosage reductions and treatment discontinuations [19, 20]. Modified FOLFIRINOX regimen involving reduced dosing have been proposed with encouraging results [15, 19], but the dose reduction was empirically chosen. Better outcome should be achieved based on rationalized mathematical model-driven protocol optimization, aiming at decreasing the toxicity of the FOLFIRINOX regimen while maintaining its efficacy. To achieve this goal, a better understanding of the PK, pharmacodynamics (PD) and

toxicity of the three drugs given in combination is mandatory. As a key step, the present review brings together for the first time the information available about population pharmacokinetic (PopPK) studies for each drug of the FOLFIRINOX combination, which will be needed for future development of pharmacokinetic/pharmacodynamic/toxicity (PK/PD/Tox) models of this polychemotherapy.

Methods

Studies selection

PopPK studies of each drug included in FOLFIRINOX regimen were systematically searched from PubMed database from inception to February 2018. The following search terms were employed: ('population pharmacokinetic' OR 'population pharmacokinetics') AND ('irinotecan' OR 'oxaliplatin' OR 'fluorouracil' OR 'folfiri' OR 'folfox' OR 'folfirinox').

Inclusion criteria

Identified studies were eligible to be included in this review if they met the following criteria:

1. Study population: human studies.
2. Treatment: one, two or three drugs from the FOLFIRINOX regimen.
3. Analysis: PopPK analysis (nonlinear mixed effect modelling) of at least one drug from the FOLFIRINOX regimen.
4. Publication in English language.

Exclusion criteria

Studies were excluded from this review if:

1. Drug administration route: other than intravenous.
2. Drug formulation: liposomal form (like PEGylated liposomal CPT 11) or prodrug of 5-fluorouracil (capecitabine).
3. Administration of anticancer drugs not included in the FOLFIRINOX regimen.

Data extraction

The following information was extracted from each included article:

1. study characteristics (e.g., types of studies, number of collected samples, dosage regimen), population characteristics (e.g., age and disease, concomitant medication)
2. information on PopPK analyses such as structural models, statistical models (i.e., inter-individual and residual variability), parameter estimates, covariates retained in the model as well as their criteria for significance, and approaches employed for model evaluation (e.g., internal or external validation).

When needed for model comparisons, additional parameters were calculated from reported data using standard PK formulae. Thus, clearance from compartment i to compartment j is equal to $V_i \times k_{ij}$. As a consequence, for exchanges between compartments i and j, intercompartmental clearance $Q_i = V_i \times k_{ij} = V_j \times k_{ji}$ and $V_j = V_i \times k_{ij}/k_{ji}$.

Simulations

PK models including only adult population and without missing parameter were used to simulate the typical PK profile for standard dose of drug in FOLFIRINOX protocol with a standard body surface area of 1.73 m^2. Simulations were performed using Simulx, a function of R package mlxR, using the reported typical value of PK parameters for the mean individual in each study. All R scripts and models used are described in Electronic Supplementary Material. The area under the concentration versus time curve (AUC) was calculated as a secondary model parameter equal to the integral of concentrations over time from zero to infinity.

Results

General overview

A PRISMA diagram describing the major steps of studies selection process is presented in Fig. 1. Studies needed to be excluded at each step because they did not fulfill the initially defined inclusion criteria. One study [21] was excluded for different reasons: 5FU concentrations were quantified from positron emission tomography data and the aim of the PopPK analysis was to determine the noise associated to this particular quantification method (residual error) rather than inter-invidual variability, as illustrated by the low number of patients (8 only). The structural model was a semi-mechanistic five-compartment model with many fixed theoretical parameters, far away from a true top-down approach. Consequently, the study was reputed irrelevant to our purpose. Conversely, the study from Mueller et al. [22] could theoretically have been excluded based on the fact that nine patients out of 31 received bevacizumab comedication. However, we decided to maintain the study in our review because bevacizumab is not a cytotoxic agent and was administered to a low proportion of the patients. Furthermore, this study was the only one to include one patient treated with FOLFIRINOX.

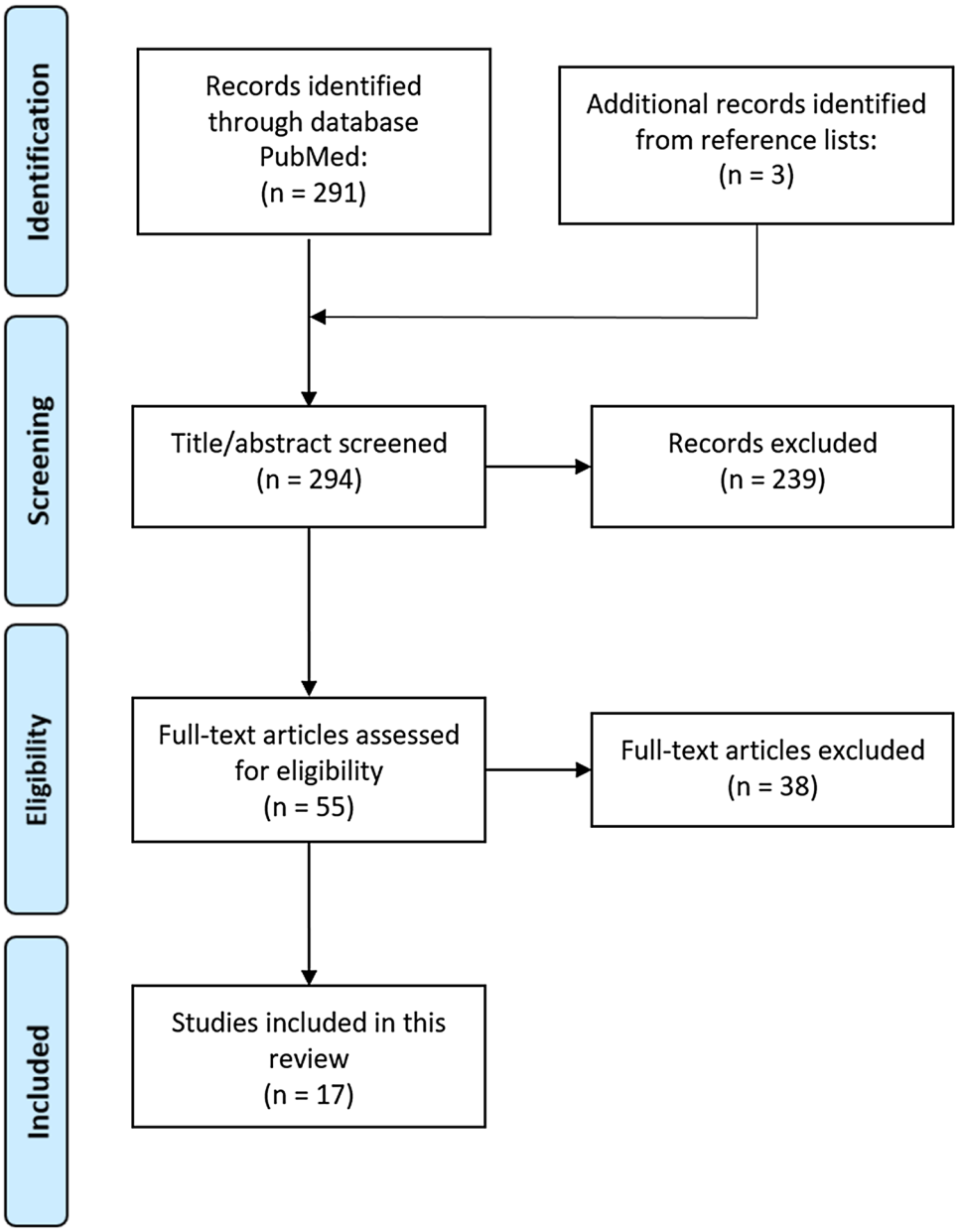

Fig. 1 PRISMA flow diagram of studies selection process

Finally, 17 publications were included in the current review: six for 5FU, six for oxaliplatin and five for CPT-11. They have been published between 1999 and 2015. The characteristics of the protocols displayed in the 17 studies are summarized in Table 1. The patients were mostly treated with only one anticancer drug of the FOLFIRINOX combination. Five studies out of 17 included patients receiving an association of two anticancer drugs of the FOLFIRINOX regimen [23–27]. None of the studies has been performed using the full FOLFIRINOX combination: only one patient in Mueller et al. received the full FOLFIRINOX regimen [22]. Cancer types were diverse. Patients were adults, except for two studies of CPT-11 [28, 29] and half the studies about oxaliplatin [30–32], which also included pediatric patients. The number of patients included in each study was generally of a few tens, ranging between 21 and 86, except for the study from Nikanjam et al. [32] which included 186 patients, due to the fact that the data originated from five different clinical studies which were pooled together for analysis. The PK data were rich in most studies, with only four studies with less than five samples per dose: two for 5FU [33, 34] and two for oxaliplatin [30, 31] which concerned pediatric populations. Tables 2, 3 and 4, respectively, summarize the characteristics of the PopPK models, the values of the model parameters, and the covariates tested and included in the PopPK models.

Table 1 Characteristics of the population pharmacokinetics studies included in the review

Author (yr)	Country	Cancer type	Patients	Adult only	Age [range]	PK samples	PK samples per dose	Dose (mg/m^2)	Duration of infusion (h)	Interval between cycles (weeks)	Comedications	Other
5-fluorouracil												
Terret (2000) [23]	France	CRC	21	x	65 [40–79]	198	10	(Bolus: 400; Infusion: 600) × D1 and D2	22	2	FA	De Gramont regimen
Mueller (2013) [22]	Switzerland	GI cancer	31	x	62.7 [31–81]	334	6	Bolus: 400; Infusion 2400	46	2	20 pts Oxa (9 + beva), 6 CPT11, 1 Oxa + CPT11	4 pts De Gramont regimen
Woloch (2012) [35]	France	CRC	127	x	61 [52–69]	741 for 5FU 865 for 5FDHU	NR	Bolus: 370 D1 to D5	NA	4	FA	
Porta-Oltra (2004) [34]	Spain	Nonmetastatic CRC	27	x	57 [36–75]	60	3	450	1	1	Levamisol	
		Metastatic CRC	17		61 [45–74]		3	425: D1 to D5	1	4	FA	
van Kuilenburg (2012) [36]	Germany	Various	30 DPD deficient, 18 Control		NR	NR	9	Bolus: 300 or 450	NA		FA	
Bressolle (1999) [33]	France	Metastatic CRC	85	x	61	562	3	(Bolus: 400; infusion: 600) × D1, D2	22	2	FA	De Gramont regimen
Oxaliplatin												
Nikanjam (2015) [32]	USA	5 pop: hepatic dys, renal dys, 3 pop of children and adolescents	186		20 [0.6–86]	1508	13	60–160	2	2 or 3	–	Age ≤ 12 months: 4.3 mg/kg
Kho (2006) [24]	The Netherlands	CRC	33	x	65 [41–76]	253	8	85	2	2	5FU (infusion ± bolus)	
Fouladi (2006) [30]	USA	Neuro-tumors	25		8.5 [0.6–18.9]		4	130	2	2–3	–	
Beaty (2010) [31]	USA	Refactory solid tumors	49		11 [1–22]		4	130	2	3		Age ≤ 12 months: 4.3 mg/kg
Delord (2003) [25]	France	CRC	40	x	59 [29–82]	780	8	80–100–130	3	2–2–3	5FU	

Table 1 (continued)

Author (yr)	Country	Cancer type	Patients	Adult only	Age [range]	PK samples	PK samples per dose	Dose (mg/m^2)	Duration of infusion (h)	Interval between cycles (weeks)	Comedications	Other
Bastian (2003) [26]	France	Metastatic cancer	56	x	59 [41–79]	537	8	50–130	2 or 4	–	5FU or CPT11	
Irinotecan and metabolites												
Berg (2015) [37]	USA	Glioblastoma or recurrent glioma	86	x	53.1	1723: 425 for irinotecan, APC; 426 for SN38, SN38G	NR	1st study: 400 (+) or 125 (−)	1.5	1	± EIAED	+: with EIAED; −: without EIAED
								2nd study: 125 (NN1) or 300 (NN3) OR 100 (N1) or 250 (N3)	1.5	1 (NN1 and N1) or 3 (N3 and NN3)	–	NN1 or NN3: no previous chemo with nitrosoureas; N1 or N3: previous chemo with nitrosoureas
Poujol (2007) [27]	France	Advanced inoperable digestive cancer	43	x	63.8 [46–84]	441	8	180 to 225	1.5	–	5FU	FOLFIRI regimen
Klein (2003) [38]	USA	Solid tumors or lymphomas	52	NR	NR	832	19	1st study: 100 to 175; 2nd study: 240 to 340	1.5	–		
Thompson (2008) [28]	USA	Solid tumors	82		10 [1–23]	NR	11	50—daily −5 days	1	3		
Kimura (2010) [29]	Japan	Solid tumors	11		11.5 [3–17]	88	7	40—D1, D2, D3, D8, D9, D10	1	3		

yr year, *PK samples* total number of pharmacokinetic samples, *5FU* 5-fluorouraci,. *CRC* colorectal cancer, *GI* gastro-intestinal, *pts* patients, *5FDHU* 5 fluoro-5,6- dihydrouracil, *pop* population, *dys* dysfunction, *EIAED* enzyme-inducing antiepileptic drugs, *FA* folinic acid, *CPT11* irinotecan, *Oxa* oxaliplatin, *beva* bevacizumab, *DPD* dihydropyrimidine deshydrogenase, *SN38* 7-Ethyl-10-hydroxy-camptothecin, *SN38G* glucuronidated SN38, *APC* 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin, D_n day, *n*, *NR* not reported, *NA* not applicable

Table 2 Population pharmacokinetics methods and models used in the included studies

Author (years)	Software	Algorithm	Molecule	Number of compartments	Elimination type		Residual variability	Validation
					Linear	MM		
Terret (2000) [23]	NONMEM V	FO	5FU	2-CPT		x	Combined: add 0.062 mg/L; prop: 10.4%	Data splitting
Mueller (2013) [22]	NONMEM VII	FOCE-I	5FU	1-CPT	x		Proportional: 25.5%	Bootstrap
			$5FUH_2$	1-CPT	x		Proportional: 33.5%	
Woloch (2012) [35]	NONMEM	FOCE-I	5FU	2-CPT	x	x	Proportional: 15%	Bootstrap
			5FDHU	1-CPT	x		Combined: add 0.56 mg/L; prop: 19%	
Porta-Oltra (2004) [34]	NONMEM		5FU	2-CPT	x		Proportional: 3%	Bootstrap
van Kuilenburg (2012) [36]	MWPharm	ITSB	5FU	2-CPT		x	Additive	External evaluation
Bressolle (1999) [33]	NONMEM IV	FO	5FU	1-CPT	x		Additive: 0.432 mg/L	Data splitting
Nikanjam (2015) [32]	NONMEM VII	FOCE-I	Oxaliplatin	3-CPT	x		Proportional: renal data 40.1% non renal data: 22.8%	Bootstrap
Kho (2006) [24]	WinNonLin	FOCE-I	Oxaliplatin	2-CPT	x		Proportional	GOF
Fouladi (2006) [30]	NONMEM V	Bayesian (POSTHOC)	Oxaliplatin	2-CPT	x		NR	GOF
Beaty (2010) [31]	ADAPT II	Bayesian	Oxaliplatin	2-CPT	x		NR	
Delord (2003) [25]	NONMEM	FO	Oxaliplatin	2-CPT	x		Proportional: 24%	
Bastian (2003) [26]	MP2		Oxaliplatin	2-CPT with EHR component	x		Proportional: 11.30%	Bootstrap
Berg (2015) [37]	NONMEM VII	IMPMAP	Irinotecan	2-CPT	x		Combined: 1st study add: 0.26 ng/mL; prop: 10.5% 2nd study: add: 0.013 ng/mL prop:14.3%	Bootstrap
			SN38	2-CPT	x			
			SN38G	1-CPT	x			
			APC	2-CPT	x			
Poujol (2007) [27]	NONMEM	Bayesian	Irinotecan	3-CPT	x		Proportional: 31.5%	Data splitting
			SN38	2-CPT	x		Proportional: 31.1%	
Klein (2003) [38]	NONMEM V	FOCE	Irinotecan	3-CPT	x		Proportional	Data splitting
			SN38	2-CPT	x			
			SN38G	1-CPT	x			
Thompson (2008) [28]	NONMEM VI	FOCE	Irinotecan	2-CPT	x		Proportional: 26.6%	External evaluation
			SN38	2-CPT	x		Proportional: 23.7%	
			SN38G	1-CPT	x		Proportional: 23,0%	
			APC	1-CPT	x		Proportional: 14.2%	
Kimura (2010) [29]	NONMEM VI	FOCE	Irinotecan	2-CPT	x		Proportional: 24.0%	Diagnostic plot

FO first-order, *FOCE* first-order conditional estimatio, *ITSB* Iterative two-stage Bayesian population procedure, *IMPMAP* Monte Carlo importance sampling EM assisted by mode a posteriori estimation, *5FU* 5-fluorouracil, *5FUH2* 5-fluoro-5,6-dihydrouracil, *5FDHU* 5 fluoro-5,6- dihydrouracil, *SN38* 7-Ethyl-10-hydroxy-camptothecin, *SN38G* glucuronidated SN38, *APC* 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin, *CPT* compartment(s), *EHR* entero-hepatic recirculation, *add* additive, *prop* proportional, *NR* not reported, *GOF* Goodness-of-fit plots

Table 3 Typical value (in bold) and inter-individual variability in % (in brackets) of pharmacokinetic parameters

(a) 5FU models	Model	CL (L/h)	V_{max} (mg/h)	K_m (mg/L)	V1 (L)	V2 (L)	Q (L/h)	k12 (h^{-1})	k21 (h^{-1})	Metabolized fraction
Terret (2000) [23]		–	**1390** (20%)	**5.57** (22%)	**12.7** (31%)	*11.9*	*67.9*	**5.35**	**5.69** (27%)	
Mueller (2013)[22]	5FU	**158** (22%)	–	–	**54.9** (19%)	–	–	–	–	**0.85**[a]
	$5FUH_2$	**126** (20%)	–	–	**120** (29%)	–	–	–	–	
Woloch (2012)[35]	5FU	**51** (43%)	**763** (63%)	**25** (60%)	**22** (50%)	**70**[a]	**6** (82%)	*0.270*	*0.0857*	
	5FDHU	**16** (68%)	–	–	**22**[a]	–	–	–	–	
Porta-Oltra (2004) [34]		**65.3** (77%)	–	–	**14.7**(82%)	**334** (138%)	**19.6** (118%)	*1.33*	*0.0587*	
van Kuilenburg (2012) [36]	Control	–	**1512** (23%)	**4.55** (14%)	**15.3** (42%)	**15.8** (18%)	**68.8** (26%)	*4.50*	*4.35*	
	DPD-deficient	–	**794** (27%)	**3.69** (22%)	**21.9** (36%)	**17.7** (26%)	**58.3** (26%)	*2.66*	*3.29*	
Bressolle (1999) [33]		**128** (56%)	–	–	**18.4** (114%)	–	–	–	–	

(b) Oxaliplatin models	CL (L/h)	V1 (L)	V2 (L)	V3 (L)	Vss (L)	Q1 (L/h)	Q2 (L/h)	k10 (h^{-1})	k12 (h^{-1})	k21 (h^{-1})	Other
Nikanjam (2015) [32]	**11.76**[c]	**22.83**[c]	**367.0**[c]	**997.1**[c]	*1387*	**67.48**[c]	**4.68**[c]	*0.52*	*3*	*0.18*	
Kho (2006) [24]	**25.2** (39%)	**41.6** (0.26%)	**452.5** (34%)	–	*494.1*	**68** (36%)	–	*0.61*	*1.6*	*0.15*	
Fouladi (2006) [30]	**12.2** (17%)	**306.9** (16%)	*399*	–	*705.9*	*3.99*	–	*0.04*	**0.013**	**0.01**	
Beaty (2010) [31]	*21.1*	**346.69**[b]	*5364*	–	*5711*	*29.5*	–	**0.061**	**0.085**	**0.0055**	
Delord (2003) [25]	**17**[d]	**21.7**[d]	**188**[d]	–	*209.7*	**33.2**[d]	–	*0.78*	*1.5*	*0.18*	
Bastian (2003) [26]	**14.1** (62%)	**24.9** (65%)	**136** (66%)	–	*160.9*	**34.8** (56%)	–	*0.57*	*1.4*	*0.26*	**ka (h^{-1}): 0.23** (391%) **k1b (h^{-1}): 1.78** **Tlag (h): 2.00** (282%)

(c) Irinotecan models	CL (L/h)	V1 (L)	V2 (L)	V3 (L)	Vss (L)	Q1 (L/h)	Q2 (L/h)	k10 (h^{-1})	k12 (h^{-1})	k21 (h^{-1})	k13 (h^{-1})	k31 (h^{-1})
Berg (2015)[37]	**43.8** (32%)	**153** (44%)	**147** (39%)	–	*300*	**27.6** (67%)	–	*0.286*	*0.180*	*0.188*	–	–
Poujol (2007) [27]	*31.7*	**12.3** (9.4%)	*102*	*153*	*267.3*	*8.59*	*193*	**2.58**[d]	**0.698** (39%)	**0.0842** (14%)	**15.7** (35%)	**1.26** (20%)
Klein (2003) [38]	*25.2*	**5.52** (26%)	*124*	*133*	*262.5*	*319*	*10.8*	**4.56** (31%)	**57.8**	**2.58**	**1.96**	**0.0812**
Thompson (2008) [28]	**34.2** (34%)	**95.5** (44%)	**101**	–	*196.5*	**23.1**	–	*0.358*	*0.242*	*0.229*	–	–
Kimura (2010) [29]	**31.7**[e] (22%)	**79.1**[e]	*107.1*	–	**186.2**[e](21%)	**6.2**[e]	–	*0.401*	*0.0784*	*0.0579*	–	–

Table 3 (continued)

(d) SN38 models	Cl_{SN38}/F_{SN38} (L/h)	$V1_{SN38}/F_{SN38}$ (L)	$V2_{SN38}/F_{SN38}$ (L)	Q_{SN38}/F_{SN38} (L/h)	$k_{SN38}10$ (h^{-1})	k_{SN38} 12 (h^{-1})	$k_{SN38}21$ (h^{-1})	Other
Berg (2015)[37]	**1760** (47%)	**270**	**26,300** (79%)	**2650** (68%)	*6.52*	*9.81*	*0.1008*	
Poujol (2007) [27]	*879.5*	**349** (37%)	*21,137*	*900.42*	**2.52** (28%)	**2.58** (13%)	**0.0426** (61%)	
Klein (2003) [38]	*785.5*	**311.7** (25%)	*13,878*	*810.47*	**2.52** (33%)	**2.6** (52%)	**0.0584**	
Thompson (2008) [28]	**302.7**[f] (46%)	**132.7**[f](47%)	**4913**[f]	**285**[f]	*2.28*	*2.14*	*0.0580*	F_{SN38}= **0.15**[a]

Italicized values: parameter calculated from reported models using standard pharmacokinetic formulae

Cl clearance, *V1* volume of the central compartment, *Vn* (with $n>1$): volume of the peripheral compartment *n*, *Vss* volume of distribution at steady-state, *ki0* elimination rate constant from compartment i, *kij* (with i and $j>0$): rate constant from compartment i to compartment j, *Q* intercompartmental clearance, *Q1* intercompartmental clearance between compartments 1 and 2, *Q2* intercompartmental clearance between compartments 1 and 3, V_{max} maximum rate of elimination, K_m the half-saturating concentration, *ka* absorption rate constant; *k1b* excretion rate constant from compartment 1 to storage site (gallbladder), *Tlag* time of drug expulsion from gallbladder, F_{SN38} fraction of irinotecan converted into SN38, Cl_{SN38}/F_{SN38} apparent clearance of SN38

[a]Fixed value

[b]200.4 L/m^2 = 346.69 L for a standard individual of 1.73 m^2

[c]Calculated for the mean value of covariates

[d]Corrected from the initial publication with the author's approval

[d]Calculated by adding k10 and k12 reported in Poujol et al.

[e]Calculated for the standard body weight of 70 kg

[f]Apparent parameters values calculated by dividing the true parameters by the F_{SN38} value, i.e., 0.15, for better model comparison

Population pharmacokinetic studies of 5-fluorouracil

Six publications reported popPK studies of 5FU (Table 1). All patients included in the studies were suffering from digestive cancers, except in Kuilenburg which included also five breast cancer patients [36]. Four studies included only patients with colorectal cancer [23, 33–35], while two also included other digestive cancer types [22, 36]. Five patients in Mueller et al. and one in Kuilenburg et al. suffered from pancreatic cancer [22, 36]. Patients received 5FU by infusion and/or bolus intravenous administration. Bolus doses varied between 300 and 450 mg/m^2, while infusion doses ranged between 425 and 2400 mg/m^2 for infusion durations of 1 and 46 h, respectively. In all studies, 5FU is associated with FA except for 27 patients in Porta-Oltra et al. [34]. The 5FU dosage from standard FOLFIRINOX protocol (i.e., bolus of 400 mg/m^2 and infusion of 2400 mg/m^2 over 46 h every 2 weeks) was used in only one study [22]. This study was the only one to combine 5FU with other anticancer drugs from the FOLFIRINOX regimen. Some patients were additionally taking bevacizumab in Mueller et al. [22] and levamisol in Porta-Oltra et al. [34]. In Kuilenburg et al. [36], four populations were distinguished, based on DPD status and dose of 5FU bolus.

PopPK structural models of 5 FU were in most cases 2-compartment models ($n=4$) [23, 34–36], but 1-compartment models have also been reported ($n=2$) [22, 33] (Table 2a). A linear elimination was presented in three publications [22, 33, 34], while a saturable Michaelis–Menten elimination was described in two articles [23, 36]. In Woloch et al., both types of elimination (linear and Michaelis–Menten) were combined [35]. Residual error for 5FU models was reported proportional in three studies [22, 34, 35], combined in 1 [23] and additive in 2 [33, 36]. The PK of 5FU metabolites was additionally described in two articles: 5FUH2 in Muller et al. [22] and 5FDHU in Woloch and al [35].

As shown in Table 3a, total 5FU clearance (CL) characterizing the linear elimination process was higher when 5FU PK was mono-compartmental (158 and 128 L/h in Mueller [22] and Bresolle [33], respectively) than when a 2-compartment model was selected (65.3 L/h in Porta-Oltra [34]). It can be explained mathematically by the fact that mono-compartmental model might have been based on PK data not allowing characterization of the slow terminal phase, then leading to an underestimation of AUC and overestimation of CL. In the two studies where a non-linear elimination model was reported, the maximum rate of elimination (V_{max}) and the half-saturating plasma concentration (K_m) values were consistent, around 1400 mg/h and 5 mg/L, respectively [23, 36]; they were lower in DPD-deficient patients [36]. The central compartment volume

Table 4 Tested and selected covariates in the PopPK models included in the review (**a** 5FU models; **b** oxaliplatin models; **c** irinotecan models)

a

	Sex	Age	BSA	Height	BW	Scr	BMI	Clcreat	Bt	Alb	Prot	TTT	Hepatic	DPD	Hepatic meta	Clock time
Terret (2000) [20]		Vmax												Vmax		
Mueller (2013) [19]	Cl						Cl									
Woloch (2012) [33]																
Porta-Oltra (2004) [31]																
van Kuilenburg (2012) [32]																
Bressolle (1999) [30]	Cl															

b

	Sex	Race	Age	BSA	Height	BW	Scr	Clcreat	GFR	Bt	Prot	Hb	TTT	PS	Hepatic	underlying malignancy
Nikanjam (2015) [29]			V1			All	Cl									
Kho (2006) [21]																
Fouladi (2006) [27]	X		X			X			X							
Beaty (2010) [28]																
Delord (2003) [22]	Cl		Cl	Cl			Cl									
Bastian (2003) [23]	Cl					X	Cl									

c

	Sex	Age	BSA	Height	BW	Scr	Bt	Alb	CRP	PS	Hepatic	Grade of D	EIAED	Cortico
Berg (2015) [34]	$_{SN38}Cl/F_{SN38}$ $_{SN38G}Cl/F_{SN38G}$											iriCl	iriCl, $_{SN38}Cl/F_{SN38}$ $_{SN38G}Cl/F_{SN38G}$	$_{APC}Cl/F_{APC}$
Poujol (2007) [24]														
Klein (2003) [35]	$_{SN38}Cl/F_{SN38}$ $_{SN38}V1/F_{SN38}$	iriCl			iriV1 $_{SN38G}V1/F_{SN38G}$		$_{SN38}V1/F_{SN38}$			iriCl $_{SN38G}Cl/F_{SN38G}$				
Thompson (2008) [25]		$_{SN38}Cl$			All		$_{SN38}Cl$							
Kimura (2010) [26]					All									

Grey box: tested covariate; parameter in the box: covariate selected on this parameter; All: allometric scaling on all parameters; x: selected covariate on not documented parameter. The information about covariates tested in Klein et al. publication is not available

BSA body surface area, *BW* body weight, *Scr* serum creatinine, *BMI* body mass index, *Clcreat* creatinine clearance, *GFR* glomerular filtration rate, *Bt* total bilirubin, *Alb* albumin, *Prot* Proteinemia, *TTT* treatment schedule, *Hb* hemoglobinemia, *CRP* creatinine reactive protein, *PS* performance status, *Hepatic* hepatic function evaluated by alanine aminotransferase, aspartate aminotransferase or lactate dehydrogenase levels, *DPD* dihydropyrimidine dehydrogenase activity, *hepatic meta* presence of hepatic metastasis, *grade of D* grade of disease, *EIAED* concomitant use of enzyme inducing anti-epileptic drug, *Cortico* concomitant use of corticosteroids

(V1) was consistently around 20 L, except in Mueller et al. [22] where a value of 54.9 L has been reported. The volumes of the peripheral compartments were close to V1, or k12 and k21 values were close, suggesting a low level of accumulation in the peripheral compartment. Interindividual variabilities of PK parameters varied tremendously between studies.

Few covariates were found to influence the elimination process, while no covariate was associated with the distribution process (Table 4a). Body surface area (BSA) [23], hepatic metastasis [23] and creatinine clearance [22] were reported once as impacting the elimination process, while two studies consistently highlighted that sex affected total 5FU clearance [22, 33].

Population pharmacokinetic studies of oxaliplatin

Six publications reported popPK studies of oxaliplatin quantified as ultrafiltrated platinum (Table 1). Delord at al. additionally studied blood oxaliplatin PK [25]. Three studies included pediatric patients in addition to adult patients [30–32]. Patients included in the studies were suffering from various solid tumor types. Two studies were performed only in adults suffering from colorectal cancer [24, 25]. Importantly, the data from Fouladi et al. [30] and Beaty et al. [31] were included in the pooled analysis by Nikanjam et al. [32]. Patients were treated by 60–160 mg/m^2 oxaliplatin over 2–4 h infusions. The oxaliplatin dosage from standard FOLFIRINOX protocol (i.e., infusion of 85 mg/m^2 over 2 h) was used in only one study [24]. In the three adult only studies [24–26], some patients received one other anticancer drug from the FOLFIRINOX regimen in addition to oxaliplatin: 5FU only in Kho et al. [24] and Delord et al. [25], 5FU or CPT-11 in Bastian et al. [26].

PopPK structural models of oxaliplatin were 2-compartment models except in Nikanjam et al. [32] where a 3-compartment model was reported (Table 2.b). Interestingly, a storage compartment was added by Bastian et al. to account for enterohepatic recirculation [26]. First-order linear

elimination was described in all studies. Residual error for oxaliplatin models was proportional when reported.

Total clearance of ultrafiltrated platinum was consistent between studies, ranging between 11.8 and 25.2 L/h (Table 3b). Volumes of each compartment varied between studies, but total volume of distribution was consistently high, the minimum value being 160.9 L (for V1 + V2) in Bastian et al. [26]. For the publication by Delord et al., the typical values of the PK parameters were recalculated independently from inter-cycle variability and for the median patient of the study population, based on the original data and model as kindly provided by the authors [25].

Influential covariates were reported in four studies [25, 26, 30, 32], and were consistent among them: renal function, as evaluated by serum creatinine or glomerular filtration rate, was shown to impact clearance, while body size, as measured by body weight or body surface area, explained total clearance or volume of distribution interindividual variabilities (Table 4b). One study included sex [26], one included age [32], and two included both sex and age [25, 30] as covariates in addition to renal function and body size.

Population pharmacokinetic studies of irinotecan

Five publications reported popPK studies of CPT-11 (Table 1) [27–29, 37, 38]. Two studies concerned paediatric population [28, 29]. Patients included in the studies were suffering from various solid tumor types. Patients suffering from lymphoma were also included in Klein et al. [38]. One publication studied FOLFIRI regimen, while other studies concerned CPT-11 in monotherapy by intravenous infusion [27]. CPT-11 dose varied between 100 and 400 mg/m^2 in adults patients. Paediatric patients received 40 or 50 mg/m^2. The CPT-11 dosage from standard FOLFIRINOX protocol (i.e., infusion of 180 mg/m^2 over 90 min) was used in one study [24]. In Berg et al., some patients received comedication by enzyme-inducing antiepileptic drugs (EIAED) and/or corticosteroids, to determine the impact of these drugs on CPT-11 PK [37].

In all studies but Kimura et al., PK of SN38, the active metabolite of CPT-11, was studied in addition to PK of CPT-11 (Table 2). Three studies additionally included SN38G PK [28, 37, 38], among which two also assessed APC PK [28, 37]. CPT-11 PK was described either by 2-compartment or 3-compartment models depending on the study. SN38 PK and SN38G were always described by a 2-compartment model and a 1-compartment model, respectively. APC PK was described once with a 1-compartment and once with a 2-compartment model. First-order linear elimination was described in all studies for CPT-11 as well as metabolites. Residual error was always proportional except for a combined error model in Berg et al.

PK parameters for CPT-11 and SN 38 are presented in Table 3c, d, respectively. Total clearances of CPT-11 were consistent between studies (Table 3c): reported values ranged between 25.2 and 43.8 L/h and values calculated as the product of V1 and k10 were 31.7 L/h and 25.2 L/h in Poujol et al. and Klein et al., respectively. Total volume of distribution was consistently high, comprised between 186.2 and 300 L with the maximum value in Berg et al. [37].

For SN38 (Table 3d), clearances and volumes are apparent parameters, normalized to the fraction of parent drug converted to SN38 (F_{SN38}). The authors have performed the normalization in three studies. For better model comparison, we performed the normalization for Thompson et al. [28] using the reported F_{SN38} value of 0.15. Since F_{SN38} value was low, apparent parameters were much higher than true parameters. Central compartment apparent volumes ranged between 132.7 and 349 L. For a F_{SN38} of 0.15, true central compartment volume would then range between 19.9 and 52.4 L, which corresponds to a free diffusion of the molecule. However, apparent peripheral volumes of distribution were between 37 and 90 times higher than central volumes, showing an extensive distribution to tissues. Total and intercompartmental apparent clearances were accordingly high, while k10 values were similar to k10 for CPT-11. Volumes and clearances were lower in the paediatric population of Thompson et al. [28], but k10 was similar.

Body weight was included in the PopPK model for allometric scaling in the two publications including paediatric population [28, 29], and as a covariate affecting CPT-11 central volume of distribution in Klein et al. [38] (Table 4c). Sex was identified twice as a covariate impacting clearance of SN38 [37, 38] and once affecting central volume of SN38 [38], while age was reported twice as impacting clearance either of CPT-11 or SN38 [28, 38]. Total bilirubin was found to influence SN38 PK in two studies [28, 38]. Berg et al. also identified the grade of disease, the concomitant use of EIAED and the presence of corticosteroids as influential covariates on CPT-11 and/or metabolites clearance [37]. Klein et al. also reported performance status as covariates for clearance of CPT-11 and SN38.

Simulations of the typical PK profiles for standard FOLFIRINOX regimen

To visualize similarities and differences between PK models, we simulated the typical PK profiles of 5FU (Fig. 2), oxaliplatin (Fig. 3) and CPT-11 and SN38 (Fig. 4) using the parameters of each adult PopPK model, with standard FOLFIRINOX protocol, i.e., 400 mg/m^2 by intravenous bolus followed by 2400 mg/m^2 intravenous infusion over 46 h for 5FU, 85 mg/m^2 infusion over 2 h for oxaliplatin and 180 mg/m^2 by infusion over 1.5 h for CPT-11. When covariates were part of the model, the typical values of PK

parameters used for simulation correspond to the values for the median individual of the population, which might differ between studies. The AUC were also calculated for each simulated curve (Fig. 5).

The typical PK profiles obtained for all the molecules were reassuringly similar between models. However, substantial variations were observed for the maximum concentration values (Cmax), and AUC values to a lesser extent (Fig. 5).

For 5FU (Fig. 2b), Cmax was similar in five models, comprised between 20 and 31 mg/L, but was much lower in Mueller et al. (10 mg/L) [22], which is to be linked to the lower central compartment volume reported in this study. In all studies, the concentration decreases to a plateau value (Fig. 2c), which is reached shortly after the bolus peak, except for Porta-Oltra et al. in which the plateau is not reached yet after 46 h [34], showing a longer terminal half-life, which might be the consequence of a high affinity toward the peripheral compartment, as shown by the high peripherical volume of distribution (V2) value (Table 3a). The plateau value was around 0.5 mg/L in most studies, but above 1 mg/L in Woloch et al. and Porta-Oltra et al., leading to higher AUC [34, 35] (Fig. 5a).

Typical PK profiles of oxaliplatin had similar shapes despite differences in the model structures (Fig. 3). The Cmax value was higher in Delord et al. [25], while AUC was higher in Nikanjam et al. [32] (Fig. 5b). The Cmax and AUC ranges were 0.8–1.6 mg/L and 5–12 mg.h/L, respectively.

CPT-11 and SN38 displayed a similar profile for the three models, but concentrations of CPT-11 and to a lesser extent of SN38 decreased faster in Berg et al., leading to lower exposure (Fig. 5c), which was ascribed by the authors to the comedication with EIAED [37].

Conclusions and perspectives

The current review first shows that few PopPK models have been published to describe the PK of FOLFIRINOX compounds. Moreover, the compounds were mostly studied in isolation and not as part of the FOLFIRINOX combination. One single patient from this review actually received the three FOLFIRINOX anticancer agents together. However, several studies suggest that there is no PK interaction between the drugs contained in the FOLFIRINOX regimen. Joel et al. studied the impact of oxaliplatin on the PK of 5FU in two studies including 18 and 10 patients, respectively, and found no significant difference in 5FU PK [39]. Similarly, no PK interaction was found between oxaliplatin and CPT-11

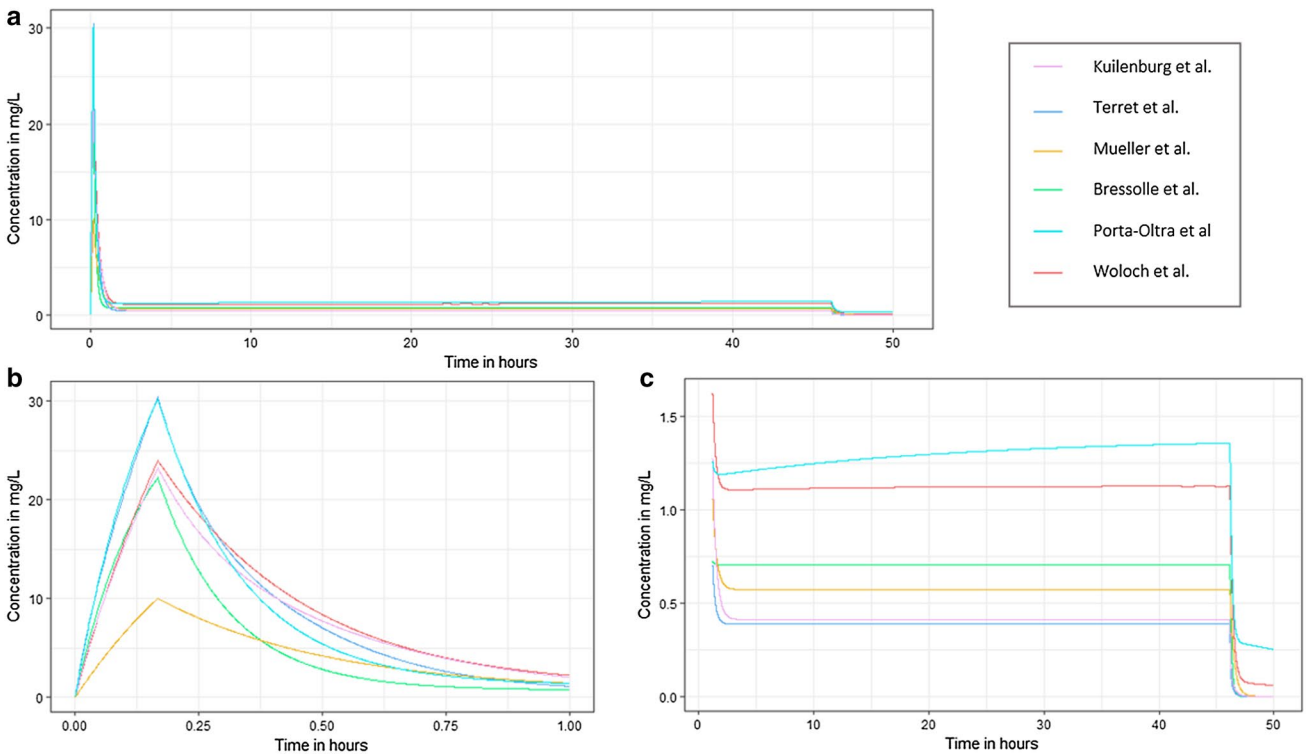

Fig. 2 Simulation of 5-fluorouracil typical PK profile after intravenous administration of a bolus of 400 mg/m^2 over 10 min and an infusion of 2400 mg/m^2 over 46 h, for a standard individual of 1,73 m^2, for all adult models included in the review. **a** Full simulation; **b** zoom on the first hour; **c** zoom after 1 h

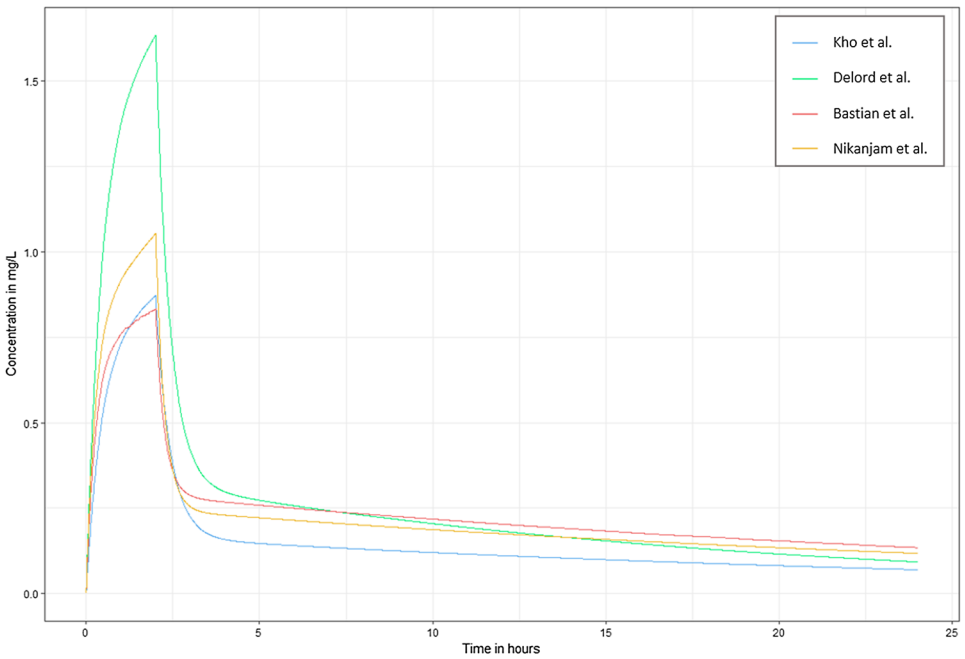

Fig. 3 Simulation of oxaliplatin typical PK profile after intravenous infusion of 85 mg/m^2 over 2 h, for a standard individual of 1.73 m^2, with all adult models included in the review

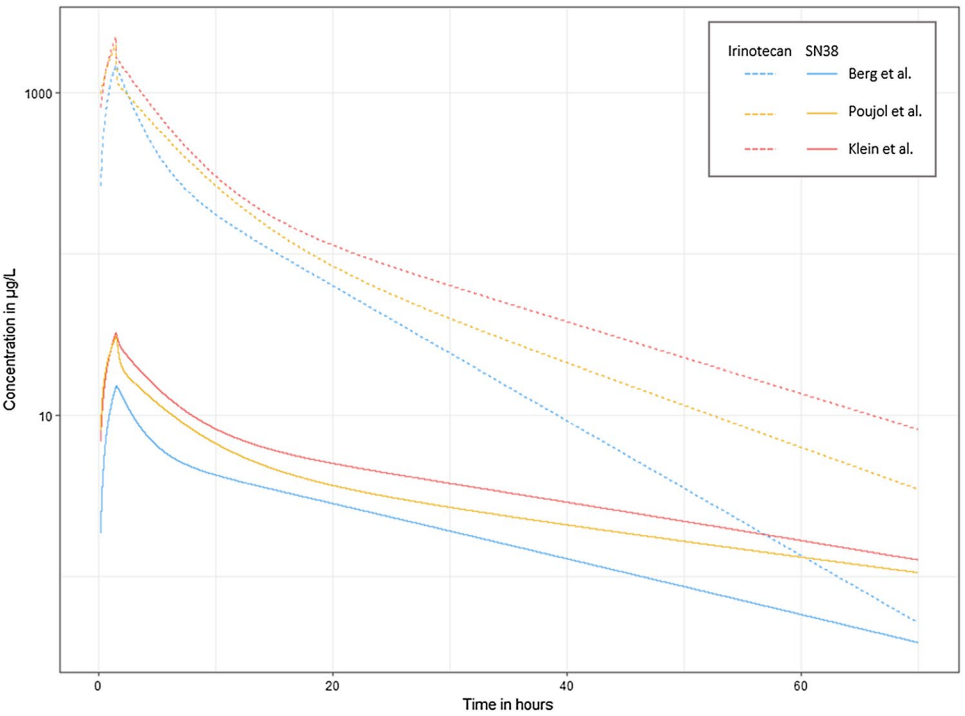

Fig. 4 Simulation of irinotecan typical PK profile after intravenous infusion of 180 mg/m^2 over 1.5 h, for a standard individual of 1.73 m^2, with all adult models included in the review. Dashed lines correspond to the pharmacokinetics of irinotecan and solid lines to the pharmacokinetics of SN38

in two phases I studies [40]. A phase I studying combination of CPT-11 and 5FU in solid tumors showed that 5FU does not impact the metabolism of CPT-11 to SN38 [41]. To the best of our knowledge, the effect of CPT-11 on 5FU PK has never been studied. The results compiled in our review are mostly in line with this statement of no interaction, since the PK profiles in the studies where two or more FOLFIRINOX agents were combined were not distinguishable from the others. However, the Cmax of 5FU was lower in Mueller et al. where patients also received oxaliplatin and/or CPT-11 [22], when compared to all other studies.

To date, treatment with FOLFIRINOX remains a standard of care in digestive cancers despite severe toxicities. These toxicities have a negative impact on efficacy because they

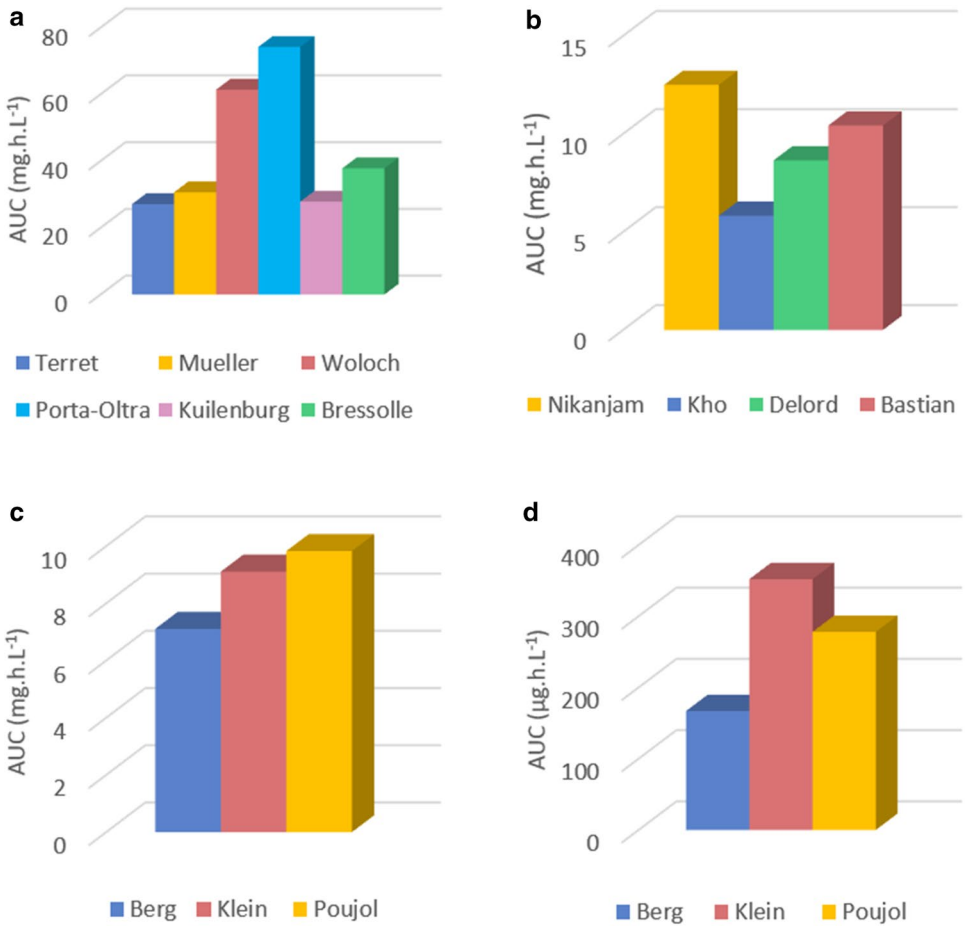

Fig. 5 Area under the concentrations versus time curved calculated as a secondary model parameter equal to the integral of concentrations over time from zero to infinity for each typical PK profile (see Figs. 2, 3, 4). **a** 5-Fluorouracil; **b** oxaliplatin; **c** irinotecan; **d** SN38

lead to empirical dosing reduction and treatment discontinuation. Since the number of potential alternate schedules is infinite, mathematical models are the only option to identify the best schedule in terms of benefit-to-risk ratio through extensive in silico testing. Few PKPD and PKTox models have been developed to date for the FOLFIRINOX compounds. For 5FU, one PKPD model described the relationship between 5FU exposure and thrombocytopenia in rats [42]. One PKPD model was developed from pre-clinical data and used to simulate tumor 5FU concentrations and tumor growth in pediatric patients, but it has not been confronted to clinical data. For CPT-11, one PKTox model described the relationship between SN38 concentrations and absolute neutrophil count [43]. For oxaliplatin, one PKPD model linked oxaliplatin concentrations after hyperthermic intraperitoneal administration to neutropenia [44]. Finally, a recent study developed a calculation tool to find an optimal "cumulative dose intensity" to conserve the efficacy and decrease toxicity of FOLFIRINOX, but the authors did not take the PK into consideration [45]. No PKPDTox model for the FOLFIRINOX regimen has been developed so far.

The current review provides a global understanding of FOLFIRINOX PK. Various PopPK models for each drug of the combination chemotherapy lead to similar typical PK profiles. The reviewed models will provide the basis for further building of a combined PKPDTox model of the FOLFIRINOX association to drive rationale-based FOLFIRINOX protocol optimization for a better outcome in cancer patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal statement This article does not contain any studies with human participants or animals performed by any of the authors.

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