Journal of Chromatography B 1236 (2024) 124039

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) methods for the therapeutic drug monitoring of cytotoxic anticancer drugs: An update

M. Briki [a,b,c], A. Murisier [a], M. Guidi [b,d,e], C. Seydoux [f], T. Buclin [b], C. Marzolini [a], F.R. Girardin [a,b], Y. Thoma [g], S. Carrara [c], E. Choong [a], L.A. Decosterd [a,*]

[a] Laboratory of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[b] Service of Clinical Pharmacology, Department of Medicine, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[c] Bio/CMOS Interfaces Laboratory, École Polytechnique Fédérale de Lausanne—EPFL, 2002 Neuchâtel, Switzerland
[d] Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, 1206 Geneva, Switzerland
[e] Centre for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[f] Internal Medicine Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[g] School of Engineering and Management Vaud, HES-SO University of Applied Sciences and Arts Western Switzerland, 1401 Yverdon-les-Bains, Switzerland

ARTICLE INFO

Keywords:
LC-MS/MS
Stable isotopically labelled internal standards
Cytotoxic drugs
Chemotherapy
Cancer
Therapeutic drug monitoring

ABSTRACT

In the era of precision medicine, there is increasing evidence that conventional cytotoxic agents may be suitable candidates for therapeutic drug monitoring (TDM)- guided drug dosage adjustments and patient's tailored personalization of non-selective chemotherapies. To that end, many liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) assays have been developed for the quantification of conventional cytotoxic anticancer chemotherapies, that have been comprehensively and critically reviewed. The use of stable isotopically labelled internal standards (IS) of cytotoxic drugs was strikingly uncommon, accounting for only 48 % of the methods found, although their use could possible to suitably circumvent patients' samples matrix effects variability. Furthermore, this approach would increase the reliability of cytotoxic drug quantification in highly multi-mediated cancer patients with complex fluctuating pathophysiological and clinical conditions. LC-MS/MS assays can accommodate multiplexed analyses of cytotoxic drugs with optimal selectivity and specificity as well as short analytical times and, when using stable-isotopically labelled IS for quantification, provide concentrations measurements with a high degree of certainty. However, there are still organisational, pharmacological, and medical constraints to tackle before TDM of cytotoxic drugs can be more largely adopted in the clinics for contributing to our ever-lasting quest to improve cancer treatment outcomes.

Contents

* Corresponding author.
E-mail address: LaurentArthur.Decosterd@chuv.ch (L.A. Decosterd).

https://doi.org/10.1016/j.jchromb.2024.124039
Received 16 November 2023; Revised 26 January 2024; Accepted 31 January 2024
Available online 03 February 2024
1570-0232/© 2024 Published by Elsevier B.V.

1. Introduction

Despite major advances in the recent years in anticancer therapies [1], conventional -cytotoxic- chemotherapeutic drugs remain in the principal first-line treatments for almost all hematological or solid cancers [2]. Due to the lasting difficulty of treating many malignancies and the inherent heterogeneity of the disease, cytotoxic drugs are not likely to be phased out any time soon [3,4].

Cytotoxic agents mostly interfere with the biochemistry of cell division, through DNA damage and mitosis interruption. More than 80 cytotoxic anticancer drugs, including natural products and derivatives thereof, have been approved by regulatory agencies [5,6]. They are generally classified with respect to their chemical family and their mechanism of action at cellular level in the categories given in Fig. 1.

Except for a few rare exceptions (e.g., L-asparaginase), cytotoxic chemotherapies are not strictly selective for tumors, as they target any rapidly dividing cells, regardless of healthy or neoplastic tissues. Thus, because of the inherent untargeted nature of cytotoxic drugs, rapidly proliferating cells such as in bone marrow are also damaged by the treatment. Weighing up the risks and benefits of treatment with cytotoxic agents constitutes a common challenge for medical oncologists. Based on clinical observations, progress in drug design, optimization of cytotoxic drug combinations, as well as supporting ancillary treatments [7], the improvements of cancer management and treatment have led to a progressive increase in treatment response and survival rates for many malignancies over the decades [8].

Despite these encouraging advances, only limited therapeutic responses have been reported for some cancers, and due to their intrinsic untargeted mechanism, cytotoxic chemotherapies can produce a number of treatment related toxicities (TRT). Cytotoxic drug dosing regimens are generally not based on formal pharmacokinetic-pharma codynamic (PK-PD) analyses during clinical trials, but have been constructed building up on the maximum tolerated dose (MTD) approach [9]. Consequently, most cytotoxic drugs have a narrow therapeutic range with considerable impact on their efficacy and tolerability. Insufficient exposure is associated with a reduced treatment efficacy and therefore higher relapse rate whereas over-exposure is related to higher TRT [10].

In general, for systemic therapies, circulating blood (or plasma) drug concentration exposure is recognized as the leading marker associated with pharmacological or toxic effects. The drug concentration in blood, rather than the dose administered, is more closely related to the exposure at the site of pharmacological action, and therefore represents a better predictor than drug dosage, for therapeutic response and/or clinical toxicity [11,12]. The determination of cytotoxic drug levels in patients' plasma has revealed a notable inter-individual variability in drug exposure, meaning that one given dosage may not result in the same systemic exposure in all patients, which is particularly true for chemotherapeutic drugs [13].

During the past decades, blood concentrations measurement has therefore been repeatedly advised to optimize the therapeutic use of various drugs, through adjustment of concentration exposure via Therapeutic Drug Monitoring (TDM) [10]. Indeed, the narrow therapeutic window constitutes a favorable argument for the use of TDM in cytotoxic treatment. As these drugs are subject to significant inter-individual PK variability, patient's outcomes could benefit from a personalized therapy [10]. It is however difficult to implement TDM systematically for all cytotoxic treatments, partly because these drugs are often administered in combination, which complicates the relationship between measurement and therapeutic outcome [14]. Some treatments are also too irregular or of too short duration and present notable intra-individual variability, making it difficult for TDM to be successfully implemented [15,16]. In addition to issues inherent to the treatments, the manipulation of cytotoxic samples necessitates specific precautions also within the analytical laboratory. This imposes a substantial workload on the laboratory staff and organizational constraints, which explains why there are only few laboratories at present that perform the TDM of cytotoxic drugs.

Applied or not in clinics due to the many obstacles evoked in the present article, TDM has nevertheless stimulated the development of numerous analytical methods to quantify a wide range of cytotoxic chemotherapeutic agents and their relevant metabolites in patients' blood [10,17–19]. Among these analytical methods, liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) stands as the gold standard, by providing unsurpassed specificity and selectivity as compared to immunoassays. LC-MS/MS methods provide similar or higher sensitivity than immunoassays, and most importantly allow, with the multiplex approach, quantifying simultaneously many drugs in the same sample [12,20].

Therefore, this review aims at presenting the published LC-MS/MS methods for the quantification of cytotoxic anticancer drugs. These assays have been developed for clinical PK studies on cytotoxic drugs disposition in the context, or in the perspective, of TDM. We will then discuss on the current limitations for the clinical implementation of TDM for cytotoxic drugs and how current analytical progress may tackle some of these issues.

2. Method of literature search

Many LC-MS/MS methods have been published over the past 24 years (1245 hits on PubMed for [(cancer) and ((cytotoxic) OR (chemotherapy)) AND (LC-MS/MS)] until 17 July 2023, no start date

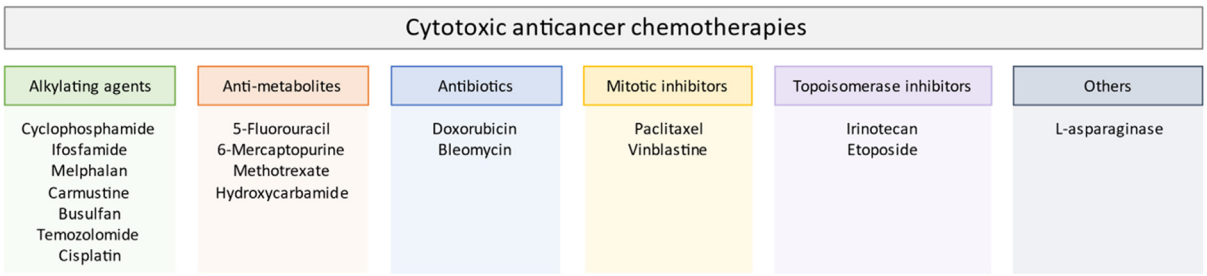

Fig. 1. Classification of cytotoxic chemotherapies. Representative examples of each chemotherapeutic class are shown.

Table 1
Overview of available LC-MS/MS methods for the quantification of cytotoxic drugs. (A) Assays designed to measure the levels of a single cytotoxic medication, as well as its associated metabolites or similar compounds within the same chemical category, and (B) Assays that utilize the capabilities of multiplex mass spectrometry analyses to simultaneously monitor multiple drugs used in either established or experimental combinations for chemotherapy. Method validation guidelines of the Food and Drug Administration (FDA), Clinical and Laboratory Standards Institute (CLSI), European Medicine Agency (EMA, ICH), Chinese Pharmacopoeia (ChPC), Comité Français d'Accréditation (French Accreditation Committee – COFRAC).

(A)

Alkylating agents

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
1	Chen et al. (2021) [21]	Busulfan (264 → 151) IS: [$^{2}H_{8}$]-busulfan	10–10,000 ng/mL	Plasma	Protein precipitation	Waters Acquity UPLC BEH C18 (2.1 mm × 50 mm, 130 Å, 1.7 μm)	Unspecified	4.5 min	Yes (EMA)
2	de Castro et al. (2016) [22]	Busulfan (264 → 150) IS: 1,6-bis(methanosulfonyloxy) hexane	3–2500 ng/mL	Plasma	Liquid-liquid extraction	Waters Novapak C18 (150 mm x 3.9 mm, 4 μm)	Unspecified	Unspecified	Unspecified
3	Ekhart et al. (2007) [23]	Cyclophosphamide (261 → 140) IS: [$^{2}H_{4}$]-cyclophosphamide	200–40,000 ng/mL	Plasma	Protein precipitation	Agilent Zorbax Extend C18 (150 mm × 2.1 mm, 5 μm) with guard column Agilent Extend C18 Narrow-Bore (12.5 mm × 2.1 mm, 5 μm)	ESI +	6 min	Yes (FDA)
		4-Hydroxycyclophosphamide semi-carbazide derivative (334 → 221) IS: hexamethylphosphoramide	50–5000 ng/mL						
4	Harahap et al. (2020) [24]	3-Hydroxypropyl mercapturic acid (222.1 → 90) IS: N-acetylcysteine	40–10,000 ng/mL	Urine	Dilution	Waters Acquity BEH C18 (2.1 × 50 mm, 1.7 μm)	ESI +	Unspecified	Yes (FDA, EMA)
5	von Stedingk et al. (2014) [25]	N-[2-(2-oxazolidonyl)ethyl]-valyl hemoglobin adduct (602.2 → 563.2; 602.2 → 460.2) IS: fluorescein-5-[4-$^{13}C_{5}$-isopropyl-3-^{15}N-(2-(2-oxazolidonyl)ethyl)-2-thioxo-imidazolidin-5-one]	4.0–400 pmol/mL	Whole blood	Protein precipitation, solid-phase extraction	Waters X-select HSS T3 (50 mm × 4.6 mm, 3 μm) or a Supelco discovery HS C18 (150 mm × 2.1 mm, 3 μm)	ESI +	Unspecified	Yes (EMA)
6	van Andel et al. (2018) [26]	Lurbinectedin (767 → 273) IS: [$^{2}H_{4}$]-lubrinectedin	0.1–100 ng/mL	Plasma	Supported liquid extraction	Achrom ACE C18 (2.1 mm × 30 mm, 3 μm)	ESI +	5 min	Yes (FDA, EMA)
			1–1000 ng/mL	Urine	Liquid-liquid extraction				
7	Egerer et al. (2010) [27] refers to Davies et al. (2000) [28]	Melphalan (305 → 168) IS: [$^{13}C_{4}$,$^{2}H_{4}$]-melphalan	2–400 ng/mL	Serum, plasma	Solid-phase extraction	Jones Chromatography Zorbax RX-C8 (150 mm x 4.6 mm, 5 μm)	ESI +	Approximately 2 min	Yes (Unspecified)
8	El Mubarak et al. (2019) [29]	Temozolomide A (195 → 138.1) B (195.2 → 138.2) IS: theophylline	Method A: 10–300 ng/mL	Plasma	Protein precipitation	Phenomenex Synergi Hydro-RP column 100 × 2 mm, 4 μm, Proguard 2–8 mm	ESI +	6 min	Yes (FDA, EMA)
			Method B: 10–500 ng/mL			Phenomenex Kinetex C18 column 100 mm × 2.1 mm, 2.1 μm with Ultra SecurityGuard pro-column		4 min	
9	Di Gregorio et al. (2020) [30]	Trabectedin (762 → 234) IS: [$^{2}H_{3}$]-trabectedin	0.01–2.5 ng/mL	Plasma	Protein precipitation	Waters Acquity BEH Amide column (2.1 mm × 100 mm, 1.7 μm)	ESI +	9.1 min	Yes (FDA)

Table 1 (*continued*)

Anti-metabolites

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
10	Donnette et al. (2023) [31]	5-Azacytidine (245.05 → 113) IS: [$^{13}C_5$]-azacytidine	5–500 ng/ml	Plasma	Protein precipitation	Waters ACQUITY UPLC C18 HSS T3 (100 mm × 2.1 mm, 100 Å)	API +	6 min	Yes (EMA)
11	Anders et al. (2016) [32]	5-Azacytidine (245.0 → 112.9) IS: 5-methyl-2′-doexycytidine	5–500 ng/mL	Plasma	Solid-phase extraction	YMC J'sphere ODS-M80 (250 mm × 2.1 mm)	ESI +	7 min	Yes (FDA)
12	Wang et al. (2021) [33]	Capecitabine (358.2 → 154.0) IS: [$^{2}H_{11}$]-capecitabine	20–15,000 ng/mL	Plasma	Unspecified	GL Sciences AQ-C18 UP (2.1 mm × 50 mm, 1.9 μm)	ESI −	3 min	Unspecified
13	Deng et al. (2015) [34]	Capecitabine (360.2 → 244.2) IS: [$^{2}H_{11}$]-capecitabine	10–5000 ng/mL	Plasma	Protein precipitation	Waters Atlantis dC18 (100 mm × 4.6 mm, 3 μm) with guard column Phenomenex C18 (4.0 mm × 3.0 mm, 5 μm)	ESI +	10.5 min	Yes (FDA, EMA)
		5′-deoxy-5-fluorocytidine (244.0 → 107.0) IS: [^{13}C,$^{15}N_2$]- 5′-deoxy-5-fluorocytidine					ESI −		
		5′-deoxy-5-fluorouridine (245.0 → 108.0) IS: [^{13}C,$^{15}N_2$]- 5′-deoxy-5-fluorocytidine							
		5-Fluorouracil (129.2 → 42.2) IS: [^{13}C,$^{15}N_2$]-5-fluorouracil	2–200 ng/mL						
14	Deenen et al. (2013) [35]	Capecitabine (360 → 130) IS: [$^{2}H_{11}$]-capecitabine	50–6000 ng/mL	Plasma	Protein precipitation (dihydro-5-fluorouracil: + solid-phase extraction)	Waters XBridge C18 (50 mm × 2.1 mm, 5 μm)	ESI +	9 min	Yes (FDA)
		5′-deoxy-5-fluorocytidine (246 → 130) IS: [^{13}C,$^{15}N_2$]-5′-deoxy-5-fluorocytidine							
		5′-deoxy-5-fluorouridine (245 → 108) IS: [^{13}C,$^{15}N_2$]-5′-deoxy-5-fluorouridine					ESI −		
		5-Fluorouracil (129 → 42) IS: [^{13}C,$^{15}N_2$]-5-fluorouracil	50–5000 ng/mL			Phenomenex Luna HILIC (150 mm × 2.1 mm, 3 μm)	ESI −	5 min	
		Dihydro-5-fluorouracil (131 → 83) IS: [^{13}C,$^{15}N_2$]- dihydro-5-fluorouracil							
		α-Fluoro-ureidopropionic acid (149 → 106) IS: [$^{13}C_3$]-α-Fluoro-ureidopropionic acid							
		Fluoro-β-alanine (106 → 86) IS: [$^{13}C_3$]- fluoro-β-alanine							
15	Reigner et al. (1999) [36]	Capecitabine (unspecified) IS: [^{13}C,$^{15}N_2$]-capecitabine	10–5000 ng/mL	Plasma	Solid-phase extraction	Supelcosil ABZ+ C18 (2.1 mm × 150 mm)	ESI	Unspecified	Unspecified
		5′-Deoxy-5-fluorocytidine (unspecified) IS: [^{13}C,$^{15}N_2$]-5′-deoxy-5-fluorocytidine							
		5′-Deoxy-5-fluorouridine (unspecified) IS: [$^{15}N_2$]-5′-deoxy-5-fluorouridine	50–25,000 ng/mL						

Table 1 (*continued*)

Anti-metabolites

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
		5-Fluorouracil (unspecified) IS: [$^{15}N_2$]-5-fluorouracil	2–1000 ng/mL			YMC JSphere M80 C18 (2.0 mm × 150 mm)			
		α-Fluoro-β-alanine (unspecified) IS: β-alanyl-alanine	20–10,000 ng/mL			YMC JSphere M80 C18 (4.6 mm × 150 mm)			
16	Tu et al. (2014) [37]	Clofarabine triphosphate (541.9 → (443.9 + 461.9)) IS: fosfomycin	1.25–100 ng/10^7 cells	PBMCs	Protein precipitation	Shiseido CAPCELL PAK CN (100 mm × 4.6 mm, 5 μm)	ESI−	3.5 min	Yes (Unspecified)
17	Abbara et al. (2020) [38]	Cytarabine (244.2 → 95) IS: [^{13}C, $^{15}N_2$]-cytarabine	100–10,000 ng/mL	Plasma	Protein precipitation	Phenomenex Kinetex HILIC column (100 mm × 2.1 mm, 2.6 μm)	ESI+	Unspecified	Yes (Unspecified)
18	Donnette et al. (2019) [39]	Cytosine-arabinoside (Cytarabine) (244.18 → 112.08) IS: [^{13}C, $^{15}N_2$]-cytarabine	1–500 ng/mL	Plasma	Protein precipitation	Waters Acquity UPLC C18 HSS T3 column (100 mm × 2.1 mm, 100 Å)	API+	6 min	Yes (FDA)
		Uracil-arabinoside (245.04 → 132.98, 112.96) IS: 5-methylcytidine	250–7500 ng/mL						
19	Chilakala et al. (2019) [40]	Decitabine (229.1 → 113.1) IS: [$^{15}N_3$]-2′-deoxycytidine	1–2000 nM	PBMCs	Hydrolysis, protein precipitation	Thermo Scientific Hypersil Gold aQ C18 (50 mm × 2.1 mm, 3 μm) with guard Hypersil Gold aQ C18 (10 mm × 2.1 mm, 3 μm)	ESI+	7 min	Yes (FDA)
		Deoxycytidine (228.1 → 112.1) IS: [$^{15}N_3$]-2′-deoxycytidine							
		5-Methyl-2′-deoxycytidine (242.0 → 126.0) IS: [$^{15}N_3$]-2′-deoxycytidine							
		Deoxyguanosine (268.0 → 152.0) IS: [$^{15}N_3$]-2′-deoxycytidine							
20	Roosendaal et al. (2019) [41]	β-Decitabine (229.1 → 113.1) IS: [$^{13}C_2$,$^{15}N_4$]-decitabine	0.5–100 ng/mL	PBMCs	Lysis	Waters Nova-Pak Silica (150 mm × 3.9 mm, 4 μm)	ESI+	14 min	Yes (FDA, EMA)
		2′-Deoxycytidine (228.0 → 112.0) IS: [^{13}C,$^{15}N_2$]-2′-deoxycytidine	50–10,000 ng/mL						
		5-Methyl-2′-deoxycytidine (242.0 → 126.0) IS: [$^2H_3$]-5-methyl-2′-deoxycytidine	5–1000 ng/mL						
21	Liu et al. (2022) [42]	5-Fluorouracil (128.8 → 42.1) IS: 5-bromouracil	10–1000 ng/mL	Serum	Liquid-liquid extraction	Agela Innoval NH_2 column (2.1 mm × 50 mm, 5 μm)	ESI−	Unspecified	Unspecified
22	Öman et al. (2021) [43]	5-Fluorouracil (128.9 → 41.7) IS: chlorodeoxyuridine	Unspecified	Plasma, intra-peritoneal fluid, wash fluid, liver, lymph nodes, pancreatic tumour, pancreatic tissue	Protein precipitation	Atlantis dC18 (2.1 mm × 100 mm, 3 μm) with an Atlantis guard column dC18 (2.1 mm × 10 mm, 3 μm)	ESI−	10 min	Unspecified
		5-Fluorodeoxyuridine (245.0 → 155.1) IS: chlorodeoxyuridine							
		5-Fluorodeoxyuridine monophosphate (325.0 → 195.0) IS: chlorodeoxyuridine							

(*continued on next page*)

Table 1 (*continued*)

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
Anti-metabolites									
		Deoxyuridine (227.1 → 184.1) IS: chlorodeoxyuridine							
		Deoxythymidine monophosphate (321.0→195.0) IS: chlorodeoxyuridine							
23	Varma et al. (2020) [44]	5-Fluorouracil (129.03 → 42.03) IS: 5-bromouracil	1–1000 ng/mL	Plasma	Protein precipitation	Xterra MS C18 column (3.9 mm × 150 mm, 5 μm)	unspecified	6 min	Yes (Unspecified)
24	Ju et al. (2016) [45] [Article in Chinese and of restricted access, only abstract available in English]	5-Fluorouracil (unspecified in abstract) IS: unspecified in abstract	49–9800 ng/mL	Plasma	Unspecified in abstract	Unspecified in abstract	Unspecified in abstract	Unspecified in abstract	Yes (FDA)
25	Derissen et al. (2015) [46]	5-fluorouridine 5′-triphosphate (500.9 → 158.9) IS: none	0.488–19.9 nM	PBMCs	Lysis	Thermo Scientific Biobasic AX (50 mm × 2.1 mm, 5 μm) with guard column 10 mm	ESI −	7 min	Yes (Unspecified)
		5-fluoro-2′-deoxyuridine 5′-triphosphate (484.8 → 256.8) IS: none	1.66–67.7 nM						
		5-fluoro-2′-deoxyuridine 5′-monophosphate (325.0 → 128.9) IS: [$^{13}C_9$,$^{15}N_2$]-uridine-5′-monophosphate	0.748–30.7 nM						
26	Büchel et al. (2013) [47]	5-Fluorouracil (131 → 114; 131 → 58) IS: [$^{15}N_2$]-5-fluorouracil	0.1–75 μM	Plasma	Liquid-liquid extraction	Waters Atlantis dC18 (2.1 mm × 150 mm, 3 μm) with guard column Waters Atlantis dC18 (2.1 mm × 10 mm, 3 μm)	ESI +	10 min	Yes (FDA)
		5-Fluoro-5,6-dihydrouracil (133 → 88; 133 → 90) IS: [$^{13}C_4$,$^{15}N_2$]-5,6-dihydrouracil	0.75–75 μM						
		Other compounds quantified in the method: uracil, 5,6-dihydrouracil							
27	Peer et al. (2012) [48]	5-Fluorouracil (128.7 → 41.4) IS: [^{13}C,$^{15}N_2$]-5-fluorouracil	8–200 ng/mL	Plasma	Liquid-liquid extraction	Supelco Discovery RP Amide C16 (150 mm × 4.6 mm, 5 μm)	API −	17 min	Yes (FDA)
		Tegafur: LC-UV (272nm)	800–20,000 ng/mL						
28	Serdar et al. (2011) [49]	5-Fluorouracil (128.0 → 41.6) IS: [$^{15}N_2$]-5-fluorouracil	0.25–250 ng/mL	PBMCs	Protein precipitation	Phenomenex Luna (150 mm × 4.6 mm, 3 μm)	ESI −	8 min	Yes (FDA)
		5-Fluoro-5,6-dihydrouracil (131.0 → 41.6) IS: [$^{15}N_2$]-5-fluorouracil	0.125–125 ng/mL						
29	Kosovec et al. (2008) [50]	5-Fluorouracil (129.0 → 41.6) IS: [$^{15}N_2$]-5-fluorouracil	10–10,000 ng/mL	Plasma	Liquid-liquid extraction	Phenomenex Shodex Asahipak NH2P-50 2D (150 mm × 2 mm, 5 μm)	ESI −	10 min	Yes (FDA)
30	Bjånes et al. (2015) [51]	Gemcitabine (264.0 → 112.0) IS: [^{13}C,$^{15}N_2$]-gemcitabine	0.125–40.0 μg/mL	Plasma	Protein precipitation	Thermo Scientific BDS HYPERSIL C18 (100 mm × 2.1 mm, 3 μm) with guard column (10 mm × 2.1 mm)	ESI +	20.3 min	Yes (Unspecified)
		2′,2′-difluoro-2′-deoxyuridine (265.1 → 112.9) IS: [^{13}C,$^{15}N_2$]-2′,2′-difluoro-2′-deoxyuridine	1.25–80.0 μg/mL						

Table 1 (*continued*)

Anti-metabolites

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
31	Bowen et al. (2009) [52]	Gemcitabine (dansyl-) (497 → 112) IS: [^{13}C,^{15}N$_2$]-gemcitabine 2,2-difluoro-2-deoxyuridine (dansyl-) (498 → 113) IS: [^{13}C,^{15}N$_2$]-2,2-difluoro-2-deoxyuridine	20–5000 ng/mL 100–25,000 ng/mL	Plasma	Liquid-liquid extraction, derivatization using dansyl-chloride	Waters BEH C18, (2.1 mm × 50 mm, 1.7 μm)	ESI +	1.5 min	Yes (Unspecified)
32	Kuriki et al. (2019) [53]	Tegafur (199.7 → 42.0) IS: 5-chlorouracil 5-Fluorouracil (128.9 → 41.9) IS: 5-chlorouracil	1–1000 ng/mL	Tears	Particular	Thermo Scientific Hypercarb (150 mm × 2.1 mm, 5 μm)	ESI −	15 min	Unspecified
33	Zhuang et al. (2013) [54]	Tegafur (198 → 41) IS: nicotinamide 5-Fluorouracil (127 → 40) IS: nicotinamide 5-chloro-2,4-dihydroxypyridine (144 → 100) IS: nicotinamide	12–3000 ng/mL 2–500 ng/mL	Plasma	Protein precipitation	Phenomenex Synergi 4u Hydro-RP 80A (150 mm × 4.6 mm, 4 μm) with guard column Phenomenex C18 (4 mm × 3.0 mm)	ESI +	Unspecified	Yes (Unspecified)
34	Hansson et al. (2021) [55]	Methotrexate (transitions not available) IS: [^{2}H$_3$]-methotrexate 7-OH-methotrexate DAMPA FA/5-Formyl-THF DHF THF 5-Methyl-THF 5, 10-Methenyl-THF Folic acid IS: [^{13}C$_6$]-folic acid	1–512 nM 1–4096 nM	Serum	Protein precipitation	Phenomenex Luna Omega Polar C18 (50 mm × 2.1 mm, 1.6 μm)	ESI +	5.1 min	Partial (EMA)
35	McTaggart et al. (2021) [56]	Methotrexate (455.2 → 134.1) IS: [^{2}H$_3$]-methotrexate	0–10 μM	Serum	Protein precipitation	Waters Phenyl Vanguard (inner diameter, 2.1 mm; particle size, 1.7 μm)	ESI +	1.5 min	Yes (FDA)
36	den Boer et al. (2013) [57]	Methotrexate monoglutamate (455.2 → 308.2) IS: [^{13}C$_5$, ^{15}N]-methotrexate monoglutamate Methotrexate diglutamate (584.4 → 308.2) IS: [^{13}C$_5$, ^{15}N]-methotrexate diglutamate Methotrexate triglutamate (713.4→308.2) IS: [^{13}C$_5$, ^{15}N]-methotrexate triglutamate Methotrexate quadriglutamate (842.4 →308.2) IS: [^{13}C$_5$, ^{15}N]-methotrexate quadriglutamate	0.97–250 nM	Erythrocytes	Protein precipitation	Waters Acquity UPLC BEH C18 (2.1 × 100 mm, 1.7 μm)	ESI +	6 min	Yes (FDA)

(*continued on next page*)

Table 1 (*continued*)

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
Anti-metabolites									
		Methotrexate pentaglutamate (971.6 →308.2) IS: [$^{13}C_5$, ^{15}N]-methotrexate pentaglutamate							
37	Rodin et al. (2013) [58]	Methotrexate (455.6 → 308.4) IS: aminopterin	2–2000 ng/mL	Saliva	Solid-phase extraction	Acclaim C18 (150 mm × 2 mm, 2.2 μm)	ESI +	<8 min	Yes (Unspecified)
38	Zhao et al. (2012) [59]	Methotrexate (455.2 → 308.2; 455.2 → 175.3; 455.2 → 134.2) IS: none	Unspecified	Serum	Solid-phase extraction	Kinetex HILIC 100 Å (100 mm × 4.6 mm, 2.6 μm)	ESI +	8 min	Unspecified
39	Han et al. (2022) [60]	6-Methylthioinosine-5′-monophosphate (378.97 → 166.92) IS: [$^2H_3$]-methotrexate 6-Methylthioinosine-5′-diphosphate (459.06 → 166.93) IS: [$^2H_3$]-methotrexate 6-Methylthioinosine-5′-triphosphate (539.10 → 167.00) IS: [$^2H_3$]-methotrexate	0.1–10 μM	Erythrocytes	Protein precipitation	Thermo Electron Biobasic AX column (2.1 mm × 50 mm, 5 μm)	ESI +	6.5 min	Yes (CLSI, EMA, FDA)
		6-Thioguanosine-5′-monophosphate (379.96 → 167.97) IS: [$^2H_3$]-methotrexate 6-Thioguanosine-5′-diphosphate (460.10 → 167.98) IS: [$^2H_3$]-methotrexate 6-Thioguanosine-5′-triphosphate (540.09 → 167.99) IS: [$^2H_3$]-methotrexate	0.025–1 μM						
40	Moon et al. (2019) [61]	6-Thioguanine (168 → 150.9) IS: [$^{13}C_2$, ^{15}N]-6-thioguanine	125–8000 ng/mL	Erythrocytes	Hydrolysis	Agilent Eclipse plus C18 (4.6 mm × 100 mm, 3.5 μm)	ESI +	5 min	Yes (Unspecified)
		6-Methylmercaptopurine (167 → 125.1) IS: [$^2H_3$]-6-methylmercaptopurine	2500–160,000 ng/mL						
41	Attallah et al. (2018) [62], based on chromatographic conditions of Al-Ghobashy et al. (2016) [63] in n°74	6-Mercaptopurine (152.89 → 119.00) Thioguanine (168.01 → 151.08)	Unspecified (QC samples at 15-100-190 ng/mL)	Plasma	Molecularly imprinted magnetic solid-phase extraction	Waters Acquity UPLC BEH shield RP (130 Å, 2.1 mm × 150 mm, 1.7 μm)	ESI +	Unspecified	Yes (ICH)
42	Coulthard et al. (2016) [64]	Deoxythioguanosine (284.19 → 168.2) IS: [$^2H_3$]-6-methylmercaptopurine Quantification of endogenous deoxyadenosine in the same method	0.000625–10 ng	DNA from nucleated blood cells	DNA digestion	Waters XSelect HSS T3 (4.6 mm × 100 mm, 3.5 μm) with guard column VanGuard cartridge (3.9 mm × 5 mm, 3.5 μm)	ESI +	8 min	Partially (FDA)

Table 1 (*continued*)

Antibiotics

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
43	Oliveira et al. (2020) [65]	Daunorubicin (528.4 → 321.1) IS: doxorubicin	0.1–1000 ng/mL 0.05–40 ng/mL 0.5–3000 ng/mL	Plasma Plasma ultrafiltrate Urine	Protein precipitation	Merck LiChrospher 60 RP-Select B (125 mm × 4.6 mm, 5 μm) with guard column LiChrospher 60 RP-Select B (4 mm × 4 mm, 5 μm)	ESI +	5 min	Yes (EMA)
		Daunorubicinol (530.3 → 383.2) IS: doxorubicin	0.1–1000 ng/mL 0.05–40 ng/mL 0.5–3000 ng/mL	Plasma Plasma ultrafiltrate Urine					
44	Harahap et al. (2020) [66]	Doxorubicin (544.22 → 397.06) IS: hexamethylphosphoramide	1–1000 ng/mL	Plasma	Protein precipitation	Waters Acquity UPLC BEH C18 (2.1 mm x 100 mm, 1.7 μm)	ESI +	7 min	Yes (EMA, FDA)
		Doxorubicinol (546.22 → 363.06) IS: hexamethylphosphoramide	0.5–500 ng/mL						
45	Pippa et al. (2020) [67]	Doxorubicin (544.3 → 397.1) IS: daunorubicin	0.4–200 ng/mL 0.4–40 ng/mL 20–8000 ng/mL	Plasma Plasma ultrafiltrate Urine	Protein precipitation (urine: dilution)	Merck LiChrospher 60 RP-Select B (250 × 4.6 mm, 5 μm) with guard column LiChrospher 60 RP-Select B (4 mm × 4 mm, 5 μm)	ESI +	Unspecified	Yes (EMA)
		Doxorubicinol (546.5 → 399.1) IS: daunorubicin	0.4–200 ng/mL 0.4–40 ng/mL 20–8000 ng/mL	Plasma Plasma ultrafiltrate Urine					
46	Yang et al. (2012) [68]	Epirubicin (544 → 397) IS: daunorubicin	Unspecified	Plasma	Liquid-liquid extraction	Agilent Zorbax SB-C18 (30 mm × 2.1 mm, 3.5 μm)	ESI +	3min	Unspecified
47	Sottani et al. (2009) [69]	Epirubicin (544 → 397) IS: trofosfamide	3–200 ng/mL	Serum	Solid-phase extraction	Thermo Electron Hypersil BDS C8 (150 mm × 4.6 mm, 5 μm)	ESI +	16 min	Yes (FDA)

Mitotic inhibitors

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (Specification)
48	de Bruijn et al. (2012) [70]	Cabazitaxel (836 → 555) IS: [$^2H_6$]-cabazitaxel	1–100 ng/mL 40–400 ng/mL	Plasma	Liquid-liquid extraction	Grace Alltima HP C18 HL (50 mm × 2.1 mm, 3 μm)	ESI +	5 min	Yes (FDA)
49	Maliszewska et al. (2023) [71]	Docetaxel (808.2 → 181.9; 808.2 → 308.8) IS: Paclitaxel	2.5–2000 ng/mL 5–2000 ng/mL	Plasma Urine	Ultrasound-assisted dispersive liquid–liquid microextraction	Phenomenex C18 Kinetex (50 mm × 2.1 mm, 1.7 μm) with guard column Phenomenex C18 (4 mm × 2 mm)	ESI +	3.5 min	Yes (FDA, ICH)
50	Vermunt et al. (2022) [72] refers to Hendrikx et al. (2013) [73]	Docetaxel (808 → 527) IS: [$^2H_9$]-docetaxel	0.25–500 ng/mL	Plasma	Liquid-liquid extraction	Agilent Zorbax Extend C18 (150 mm × 2.1 mm, 5 μm)	ESI +	9 min	Yes (FDA)
		Docetaxel-M1 (839 → 527) (IS: [$^2H_9$]-docetaxel) Docetaxel-M2 (824 → 298) (IS: [$^2H_9$]-docetaxel) Docetaxel-M3 (839 → 527) (IS: [$^2H_9$]-docetaxel)	Use of docetaxel calibration						

(*continued on next page*)

Table 1 (*continued*)

Mitotic inhibitors

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (Specification)
		Docetaxel-M4 (837 → 527) (IS: [$^{2}H_{9}$]-docetaxel)							
	Vermunt et al. (2011) [72] refers to Hendrikx et al. (2011) [74]	Docetaxel (808 → 527) IS: [$^{2}H_{9}$]-docetaxel Paclitaxel (854 → 509) IS: [$^{13}C_{6}$]-paclitaxel Other non-cytotoxic compound in the same method: ritonavir	0.5–500 ng/mL	Plasma	Liquid-liquid extraction	Agilent Zorbax Extend C18 (150 mm × 2.1 mm, 5 μm)	ESI +	9 min	Yes (FDA)
51	Jones et al. (2012) [75], ThermoFisher Documentation	Docetaxel (830.26 → 549.24) IS: paclitaxel	0.25–10 ng/mL	Serum	Solid-phase extraction	Thermo Scientific Accucore RP-MS (50 mm × 2.1 mm, 2.6 μm)	ESI +	2 min	Unspecified
52	Yang et al. (2020) [76]	Docetaxel (830.3 → 548.8) IS: paclitaxel	1–500 ng/mL	Plasma	Hybrid solid-phase extraction-protein precipitation	Agilent Zorbax Eclipse Plus C18 (150 × 2.1 mm, 3.5 μm)	ESI +	8.1 min	Yes (ChPC, FDA)
53	Gao et al. (2014) [77]	Docetaxel (830.4 → 303.9) IS: vindoline	10–1000 ng/mL	Plasma	Liquid-liquid extraction	Agilent Zorbax SB-C18 (100 mm × 2.1 mm, 3.5 μm)	ESI +	4.5 min	Yes (Unspecified)
		Paclitaxel (876.4 → 308.0) IS: vindoline	25–2500 ng/mL						
		Vinblastine (811.5 → 224.2) IS: vindoline	10–1000 ng/mL						
		Vinorelbine (779.3 → 122.1) IS: vindoline							
54	Guitton et al. (2005) [78]	Docetaxel (808.4 → (527.2 + 509.2)) IS: paclitaxel	0.5–1000 ng/mL	Plasma	Liquid-liquid extraction	Waters SunFire C18 (100 mm × 2.1 mm, 3.5 μm) with guard column SunFire guard cartridge (10 mm × 2.1 mm)	ESI +	10 min	Yes (Unspecified)
		Docetaxel-M1 (822.4 → (527.2 + 509.2)) IS: paclitaxel							
		Docetaxel-M2 (824.4 → 298.1)							
		Docetaxel-M3 (822.4 → (527.2 + 509.2)) IS: paclitaxel							
		Docetaxel-M4 (820.4 →(527.2 + 327.1)) IS: paclitaxel							
55	Morgan et al. (2015) [79]	Eribulin (730.5 → 712.5) IS: ER-076349	LLOQ: 0.1 ng/mL	Plasma Urine	Liquid-liquid extraction	C18 (unspecified)	Unspecified	Unspecified	Yes (Unspecified)
56	Christner et al. (2019) [80]	Paclitaxel (854.5 → 286.0) IS: [$^{13}C_{6}$]-paclitaxel	10–10,000 ng/mL	Plasma	Liquid-liquid extraction	Phenomenex Synergi Polar-RP (2 mm × 50 mm, 4 μm)	ESI +	8 min	Yes (FDA)
		3-para-OH-paclitaxel (870.5 → 569.5)	1–1000 ng/mL						
		6-alpha-OH-paclitaxel (870.5 → 286.0) IS: [$^{2}H_{5}$]-6-alpha-OH-paclitaxel							

Table 1 (*continued*)

Mitotic inhibitors

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (Specification)
57	Fernández-Peralbo et al. (2014) [81]	Paclitaxel (876.0 → 308.0) IS: docetaxel	0.125–100 ng/mL 0.21–750 ng/mL	Serum (plasma) Peritoneal tissue	Liquid-liquid extraction	Teknokroma Mediterranea Sea C18 (50 mm × 4.6 mm, 3 μm)	ESI +	17.5 min	Unspecified
		6α-OH-paclitaxel (892.0 → 607.0) IS: docetaxel	0.5–100 ng/mL 0.5–450 ng/mL	Serum (plasma) Peritoneal tissue					
		C3′–OH-paclitaxel (892.0 → 324.0) IS: docetaxel	0.125–100 ng/mL 0.21–450 ng/mL	Serum (plasma) Peritoneal tissue					
58	Bulitta et al. (2009) [82,83]	Paclitaxel (854 → 286) IS: [$^{13}C_6$]-paclitaxel	0.1–50 ng/mL 5–5000 ng/mL	Plasma ultrafiltrate Whole blood	Liquid-liquid extraction	Phenomenex Curosil-PFP (50 mm × 2 mm, 3 μm)	ESI +	2.9 min	Yes (Unspecified)
59	Kłys et al. (2007) [84]	Vinblastine (811 → 793; 811 → 751) IS: vincristine	1–20 ng/mL 10–100 ng/mL	Whole blood Liver biopsy	Liquid-liquid extraction	Merck LiChroCART Purospher RP 18 (125 mm × 3 mm, 5 μm) with guard column LiChroCART LiChrospher 60 RP—select B (4 mm × 4 mm, 5 μm)	APCI +	25 min	Yes (Unspecified)
60	van der Heijden et al. (2023) [85]	Vincristine (825.2 → 765.4) IS: [$^{2}H_3$]-vincristine sulphate	1–50 ng/mL	Whole blood	Solid-liquid extraction	Phenomenex Gemini C18 (50 mm × 2.0 mm, 5 μm)	ESI +	5 min	Yes (FDA, EMA)
61	Yan et al. (2012) [86]	Vincristine (825.8 → 807.5) IS: vinblastine	0.5–800 ng/mL	Plasma	Liquid-liquid extraction	Agilent Eclipse XDB C18 (50 mm × 4.6 mm, 5 μm)	ESI +	5.5 min	Yes (Unspecified)
62	Guilhaumou et al. (2010) [87]	Vincristine (825.4 → 765.4) IS: vinblastine	0.25–50 ng/mL	Plasma	Solid-liquid extraction	Phenomenex Luna C8 (50 mm × 2.0 mm, 3.0 μm)	ESI +	8 min	Yes (FDA)
63	Corona et al. (2018) [88]	Vinorelbine (779.6 → 122.4) IS: [$^{2}H_3$]-vinorelbine 4-O-deacetylvinorelbine (737.3 → 122.4) IS: [$^{2}H_3$]-4-O-deacetylvinorelbine	0.05–25 ng/mL	Whole blood	Protein precipitation	Phenomenex Onyx monolith C18 (50 mm × 2 mm)	ESI +	6 min	Yes (FDA)
64	Di Desidero et al. (2016) [89]	Vinorelbine (390.3 → 122.2) IS: vinblastine	Unspecified	Plasma	Protein precipitation	Waters Acquity UPLC BEH C18 (2.1 mm × 50 mm, 1.7 μm) with guard column Waters Vanguard BEH C18 1.7 μm	ESI +	Unspecified	Unspecified
65	Bourgeois et al. (2007) [206] refers to van Heugen et al. (2001) [90]	Vinorelbine (779 → 122) IS: vinblastine	0.25–200 ng/ml 0.5–200 ng/ml 2–1000 μg/g 2.5–1000 ng/ml	Whole blood Plasma Feaces Urine	Protein precipitation Dilution	Spherisorb CN (100 mm × 4.6 mm, 3 μm) with guard column Spherisorb CN (10 mm × 2 mm)	ESI +	20 min	Yes (Unspecified)
		4-O-Deacetylvinorelbine (737 → 122) IS: vinblastine	0.25–50 ng/ml 0.5–50 ng/ml 2–1000 μg/g 2.5–250 ng/ml	Whole blood Plasma Feaces Urine	Protein precipitation Dilution				
		20′-Hydroxyvinorelbine (795 → 138) IS: vinblastine	2.5–50 ng/ml 2.5–50 ng/ml undefined-1000 μg/g 12.5–250 ng/ml	Whole blood Plasma Feaces Urine	Protein precipitation Dilution				
		Vinorelbine 6′-oxide (795 → 138) IS: vinblastine	10–50 ng/ml 10–50 ng/ml undefined-1000 μg/g 50–250 ng/ml	Whole blood Plasma Feaces Urine	Protein precipitation Dilution				

Table 1 (*continued*)

Topoisomerase inhibitors

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
66	Atasilp et al. (2018) [91]	Irinotecan (587.3 → 167.0) IS: camptothecin	5–10,000 ng/mL	Plasma	Protein precipitation	Phenomenex Kinetex C18 (50 mm × 2.1 mm, 1.7 μm)	ESI+	18 min	Yes (FDA)
		SN-38 (392.9 → 349.1) IS: camptothecin	5–1000 ng/mL						
		SN-38G (569.0 → 393.3) IS: camptothecin	8–1000 ng/mL						
67	Calandra et al. (2016) [92] refers to Marangon et al. (2015) [93]	Irinotecan (587.4 → 124.2) IS: camptothecin	10–10,000 ng/mL	Plasma	Protein precipitation	Phenomenex Gemini C18 (100 mm × 2.0 mm, 3 μm) with guard column Gemini-NX C18 (4.0 × 2.0 mm)	ESI+	18 min	Yes (FDA, EMA)
		SN-38 (393.3 → 349.3) IS: camptothecin	1–500 ng/mL						
		SN-38G (569.3 → 393.2) IS: camptothecin							
		APC (619.2 → 393.3) IS: camptothecin	1–5000 ng/mL						
68	Herviou et al. (2016) [94]	Irinotecan (587.3 → 124.1) IS: camptothecin	25–2500 ng/mL	Plasma	Protein precipitation	Thermo Scientific Hypersil GOLD (50 mm × 2.1 mm, 3 μm)	ESI+	10.92 min	Yes (EMA, COFRAC)
		SN-38 (393.2 → 349.3) IS: camptothecin	5–500 ng/mL						
69	Ramesh et al. (2010) [95] Review of analytical methods for irinotecan and its metabolites								
	D'Esposito et al. (2008) [96]	Irinotecan (587 → 124) IS: camptothecin	1.56–25 ng/mL 1.56–100 ng/mL	Plasma Liver microsomes	Solid-phase extraction	Alltima C18 (150 ×2.1 mm, 5 μm) with guard column Alltima C18 (7.5 × 2.1 mm, 5 μm)	ESI+	7 min	Yes (Unspecified)
		SN-38 (393 → 349) IS: camptothecin	3.13–150 ng/mL	Plasma Liver microsomes					
		APC (619 → 227) IS: camptothecin	0.78–25 ng/mL 0.78–100 ng/mL	Plasma Liver microsomes					
	Khan et al. (2003) [97]	SN-38 (393.1 → 349.2) IS: camptothecin	0.05–400 ng/mL	Plasma	Protein precipitation	Synergy Hydro-RP C18 (50 × 2 mm, 4 μm)	ESI+	3 min	Yes (FDA)

Table 1 (*continued*)

Miscellaneous compounds

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
70	Janssen et al. (2019) [98]	Vorinostat (265.2 → 232.0) IS: [$^{13}C_6$]-vorinostat Other non-cytotoxic drugs quantified using the same method: alectinib, lenvatinib, nintedanib, vismodegib, cobimetinib, palbociclib, osimertinib, ribociclib	25–500 ng/mL	Plasma	Protein precipitation	Phenomenex Gemini C18 column (50 mm × 2.0 mm, 5.0 μm) with Gemini C18 guard column (4 mm × 2.0 mm, 5.0 μm)	ESI +	4 min	Yes (FDA, EMA)
71	Burhenne et al. (2017) [99] refers to Liu et al. (2014) [100]	Vorinostat (265 → 232) IS: [$^{2}H_5$]-vorinostat	11–1100 ng/mL	Plasma	Solid-phase extraction	Phenomenex Luna C18 (150 mm × 2 mm, 3 μm, 100 A)	ESI +	16 min	Yes (FDA, EMA)
		4-Anilino-4-oxobutanoic acid (194 → 176) IS: [$^{2}H_5$]-4-anilino-4-oxobutanoic acid	11–11,000 ng/mL						
		Vorinostat-O-glucuronide (441.3 → 265.1) IS: [$^{2}H_5$]-vorinostat-glucuronide							
		Vorinostat (265 → 232) IS: [$^{2}H_5$]-vorinostat	0.1–10 ng/3 × 10^6 cells	PBMCs	Liquid-liquid extraction				
		4-Anilino-4-oxobutanoic acid (194 → 176) IS: [$^{2}H_5$]-4-anilino-4-oxobutanoic acid							
		Vorinostat-O-glucuronide (441.3 → 265.1) IS: [$^{2}H_5$]-vorinostat-glucuronide							
72	Suresh et al. (2017) [101] Review of analytical methods for histone deacetylase inhibitors vorinostat, belinostat, panobinostat, romidepsin and chidamide								
	Gu et al. (2015) [102]	Chidamide (391.1 → 265.1) IS: MS-275	1–1000 ng/mL	Plasma	Protein precipitation	Thermo Electron Hypersil GOLD C18 (2.1 mm × 100 mm, 5 μm)	ESI +	7 min	Yes (Unspecified)
	Refers to Liu et al. (2014) [100] as described in n°71								
	Kiesel et al. (2013) [103]	Belinostat (319 → 93) IS: [$^{13}C_6$]-belinostat	30–5000 ng/mL	Plasma	Protein precipitation	Acquity UPLC BEH (50 mm × 2.1 mm, 1.7 μm)	ESI +	7 min	Yes (FDA)
		Belinostat-glucuronide (495.3 → 319.1)							
		Methyl-belinostat (333.1 → 93)							
		Belinostat-M24 (278.1 → 92) IS: [$^{2}H_5$]-M24					ESI −		
		Belinostat-amide M21 (301.1 → 92)							
		Belinostat-acid M26 (302.1 → 92.2)							
	Wang et al. (2010) [104]	Belinostat (319 → 93) IS: oxamflatin	0.5–1000 ng/mL	Plasma	Liquid-liquid extraction	Thermo Electron Hypersil BDS C18 (2.1 mm × 100 mm, 5 μm)	ESI +	6 min	Yes (referring to FDA guidelines)

(*continued on next page*)

Table 1 (*continued*)

Miscellaneous compounds

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)
	Patel et al. (2008) [105]	Vorinostat (265.2 → 232.1) IS: [$^2H_5$]-vorinostat	1–1000 ng/mL	Serum	Protein precipitation	Phenomenex Gemini C18 (150 mm × 2.0 mm, 3 μm) with guard column	ESI +	14 min	Yes (unspecified)
		Decitabine (229 → 113) IS: 2′-azido-2′-deoxyuridine	2–2000 ng/mL			Phenomenex Gemini C18 (4.0 mm × 2.0 mm, 3 μm)			
	Parise et al. (2006) [106]	Vorinostat (265.2 → 232.2) IS: [$^2H_5$]-vorinostat Vorinostat-glucuronide (441.2 → 265.2, 232.2) IS: [$^2H_5$]-vorinostat-glucuronide 4-anilino-4-oxobutanoic acid (194 → 176.2) IS: [$^2H_5$]- 4-anilino-4-oxobutanoic acid	3–1000 ng/mL	Serum	Protein precipitation	Thermo Electron Hypersil BDS C18 (100 mm × 3 mm, 3 μm)	ESI +	20 min	Yes (unspecified)
	Du et al. (2005) [107]	Vorinostat (265.1 → 232.1) IS: [$^2H_5$]-vorinostat	2–500 ng/mL	Serum	Turboflow HTLC extraction column Cyclon (0.5 × 50 mm, 60 μm)	Thermo Scientific Hypersil BDS C18 (2.1 mm × 30 mm, 3 μm)	ESI +	6 min	Yes (unspecified)
		Vorinostat-glucuronide (441.1 → 232.1) IS: [$^2H_5$]-vorinostat-glucuronide	5–2000 ng/mL						
		4-anilino-4-oxobutanoic acid (194.1 → 175.9) IS: [$^2H_5$]- 4-anilino-4-oxobutanoic acid	10–2000 ng/mL						

(B)
Combinations for treatment regimens

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)	Treatment regimen examples
73	Qi et al. (2023) [108]	Pirarubicin (628.6 → 397.2) IS: Pioglitazone	1–500 ng/mL	Plasma	Liquid-liquid extraction	Agilent Eclipse XDB-C18 (3.0 mm × 100 mm) with guard column Shim-pack GVP-ODS (2.0 mm × 5 mm, 2.2 μm)	ESI +	8 min	Yes (unspecified)	CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP: incl. rituximab) CAP: doxorubicin, cyclophosphamide, cisplatin
		Doxorubicin (544.5 → 397.2) IS: Pioglitazone	2–1000 ng/mL							
		Cyclophosphamide (261.1 → 140.1) IS: Pioglitazone	2.5–1250 ng/mL							
		Vincristine (825.4 → 144.1) IS: Pioglitazone	3–1500 ng/mL							
74	Al-Ghobashy et al. (2016) [63]	Methotrexate (455.34 → 308.22) IS: thiouracil 6-Mercaptopurine (152.89 → 119.00) IS: thiouracil 6-Thioguanine (168.01 → 151.08) IS: thiouracil	6.25–200 ng/ml	Plasma	Solid-phase extraction	Waters Acquity UPLC BEH shield RP 130 Å (2.1 mm × 150 mm, 1.7 μm)	ESI +	1.4 min	Yes (FDA)	Methotrexate improves 6-mectaptopurine bioavailability and is used in association [109]

Table 1 (*continued*)

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)	Treatment regimen examples
75	Shu et al. (2016) [110]	Cyclophosphamide (261.0 → 140.0) IS: fluconazole	2–2000 ng/mL	Serum	Solid-phase extraction	Waters XBridge® BEH C18 (2.1 mm × 50 mm, 2.5 μm)	ESI +	10 min	Yes (FDA, ChPC)	VCD: cyclophosphamide, bortezomib, dexamethasone AC: Adriamycin (doxorubicin), cyclophosphamide VRD: bortezomib, lenalidomide, dexamethasone PAD: bortezomib, Adriamycin (doxorubicin), dexamethasone CTD: cyclophosphamide, thalidomide, dexamethasone VTD: bortezomib, thalidomide, dexamethasone
		Adriamycin (doxorubicin) (544.2 → 397.0) IS: vindoline	2–2000 ng/mL							
		Other drugs quantified using the same method: bortezomib, thalidomide, lenalidomide, dexamethasone								
76	Lee et al. (2016) [111]	Tipiracil (unspecified) IS: stable isotope (unspecified)	0.8–200 ng/mL	Plasma, urine	Solid-phase extraction	Inertsil ODS-3 (2.1 mm × 150 mm)	ESI (unspecified)	Unspecified	Yes (FDA)	TAS-102: tipiracil, trifluridine
		Other drugs quantified using the same method: trifluridine, trifluoromethyluracil			Liquid-liquid extraction	Capcell PAK C18 AQ (2.0 mm × 150 mm)				
77	Zhou et al. (2012) [112]	Cyclophosphamide (261.0 → 140.1) IS: vindoline	1–1000 ng/mL	Plasma	Protein precipitation, liquid–liquid extraction	Waters Atlantis T3-C18 (2.1 mm × 100 mm, 3 μm)	ESI +	18 min	Yes	VIP: cisplatin, etoposide, ifosfamide GemCarbo: gemcitabine, carboplatin CECA: cyclophosphamide, etoposide, carboplatin, cytarabine ICE: ifosfamide, carboplatin, etoposide ACE: doxorubicin, cyclophosphamide, etoposide
		Ifosfamide (260.7 → 154.0) IS: vindoline								
		Irinotecan (587.1 → 167.1) IS: vindoline	10–10,000 ng/mL							
		Etoposide (589.0 → 229.1) IS: vindoline	5–5000 ng/mL							
		Gemcitabine (264.1 → 112.0) IS: vindoline	50–5000 ng/mL							
		Carboplatin (372.2 → 294.1) IS: vindoline								
		Pemetrexed (428.3 → 281.2) IS: vindoline	100–10,000 ng/mL							

(*continued on next page*)

Table 1 (*continued*)

N°	Reference	Analyte (quantifier transition(s)) IS: internal standard	Calibration range	Matrix	Extraction method	Column	Ionization mode	Method duration	Validated method (specification)	Treatment regimen examples
78	Skolnik et al. (2006) [113]	Actinomycin-D (1255.6 → 858.3) IS: 7-amino-actinomycin-D Vincristine (825.4 → 766.4) IS: vinblastine	0.5–100 ng/mL	Plasma	Solid-phase extraction	Phenomenex Luna RP C8 (50 mm × 2 mm, 3 μm)	ESI+	18 min	Yes (unspecified)	VAI: vincristine, actinomycin D, ifosfamide
79	De Jonge et al. (2004) [114]	Cyclophosphamide (261 → 140) IS: hexamethylphosphoramide 4-Hydroxycyclophosphamide semi-carbazide derivative (334 → 221) IS: hexamethylphosphoramide Thiotepa (190 → 147) IS: hexamethylphosphoramide Tepa (174 → 131) IS: hexamethylphosphoramide	200–40,000 ng/mL 50–5000 ng/mL 5–2500 ng/mL	Plasma	Protein precipitation	Agilent Zorbax Extend C18 (150 mm × 2.1 mm, 5 μm) with guard column Agilent Extend C18 narrow-bore (12.5 mm × 2.1 mm, 5 μm)	ESI+	10 min	Yes (FDA)	CTC: cyclophosphamide, thiotepa, carboplatin

specified). For this review, only publications reporting LC-MS/MS methods for the quantification of cytotoxic compounds in human biological matrices have been retained. Compounds that are not used in clinical practice, i.e., investigational compounds subjected to clinical trials, were not considered in this review.

3. Result and discussion

3.1. LC-MS/MS methods

A total of 88 articles describing or applying LC-MS/MS methods for the quantification of various anticancer cytotoxic compounds were retained. From these articles, comprising reviews as well, 90 analytical methods were retrieved from 79 articles and were classified into two categories: A) Assays for quantifying a single cytotoxic drug, and their relevant metabolites, or analogous compounds belonging to the same chemical class; B) Assays exploiting the power of multiplex mass spectrometry analyses [12] for monitoring simultaneously several drugs part of conventional, or experimental chemotherapeutic combination regimens. The methods and their main technical characteristics are classified with respect to the respective anticancer drugs' category (Fig. 1) and reported in alphabetic order and descending chronological order in Tables 1A and 1B, respectively. The analytical and clinically relevant features comprise: i) analyte name and relevant metabolite, as well as the mass-to-charge ratio (m/z) transitions used and the internal standard (IS) used; ii) the concentration range of quantification that should encompass the drug concentrations typically observed in patients; iii) the biological matrix; iv) the sample preparation method; v) LC-MS/MS parameters such as the chromatographic column, the ionisation mode and the analytical run time; vii) the official guidelines followed when the methods have been formally validated. For Table 1B, the abbreviated chemotherapeutic combination regimens have been added.

3.2. Current practices for the LC-MS/MS analyses of cytotoxic drugs and/or their metabolites in humans

3.2.1. Biological matrices and sample extraction

The review of the different LC-MS/MS methods used to analyze cytotoxics has shown that, as for most drugs, plasma and serum are the most widely used biological matrices (82 % of the methods reviewed). Alternate matrices such as plasma ultrafiltrate (i.e., unbound drug level), whole blood, urine, tears, saliva, cells (erythrocytes and peripheral blood mononuclear cells (PBMCs)), and finally solid materials (faeces and biopsies) have been also subjected to analyses, though in only very few studies.

The rationale behind choosing a matrix over another for drug quantification is multiple and includes i) the pharmacological relevance of measuring the cytotoxic drugs in a given body compartment, ideally at the ultimate (generally profound) target of expected cytotoxic activity; ii) the medical constrains of the invasiveness of specimen collection procedure and associated patient discomfort.

Plasma and serum are the more frequent matrices found in this review and are logistically convenient, as blood obtained by venous blood puncture is a limitedly invasive procedure with minimal patient discomfort. In some instances, such procedure can be alleviated by capillary blood sampling performed from the finger in adult patient (or sides of the heel in paediatric and neonatal patients) that is blotted and dried onto dried blood spot (DBS) filter paper [115].

Generally, plasma and/or serum are preferred over whole blood because these matrices are less viscous and more easily amenable to samples preparation [116]. Furthermore, essentially all PK target ranges of drug exposure, when available, have been mostly established in plasma or serum [10].

In addition, TDM is generally based on total plasma concentration measurements while the free (i.e., unbound) circulating plasma level constitutes the only fraction likely to cross tumour cell membrane to exert its intracellular pharmacological -cytotoxic- activity. In that respect, the LC-MS/MS technology is sensitive enough to also quantify the unbound drug fraction, even for drugs that are highly bound to circulating plasma proteins. For instance, the measurement of not only total but also free plasma levels have been notably documented for doxorubicin [67] that is up to 85 % bound to plasma proteins [117].

Drugs levels measured in plasma *a fortiori* directly reflect the extracellular environment to which hematological cancer cells are exposed. It is also assumed that the drugs concentration measured in plasma is the more easily accessible and best available proxy of drug levels in the interstitial fluid environment surrounding solid tumours. However, alteration of pH in the extracellular medium may influence tissue cell penetration, which also depends on drug's pKa [118]. In addition, cell membrane of target malignancies may undergo genetic and environmental changes that can alter cytotoxic drugs disposition in tumour cell, notably by alteration of transmembrane drug resistance transporters expression (i.e., multidrug resistance pump) [119]. However, drug levels measured in tumors can be of clinical interest as reported for platinum, whose tissue concentration (measured by atomic absorption spectrophotometry) was found to be significantly associated with tumour size reduction in non-small cell lung cancer (NSCLC) patients [120]. Nevertheless, with the LC-MS/MS technology, there are very limited reports of quantification of cytotoxics in target cancer cells (3 % of the retrieved methods), including one post-mortem case [84]. Medical constraints of invasive tumour biopsies collection, which are generally performed for cancer cell typing, *prior* to chemotherapies, are limiting this application to pre-operative [43] or intra-operative [81] chemotherapies.

In some cases, determination in whole blood is more appropriate than in plasma. This is the case for vinorelbine, which binds primarily to platelets and blood cells and is therefore quantified in whole blood [88,90,121], with some exceptions where quantification in plasma may be more practical as part of a multiplexed assay for example [77]. For the widely investigated case of thiopurines, the assay is carried out in red blood cell (RBCs). For this, whole blood can be frozen for directly hemolyzing RBCs or centrifuged to isolate RBCs from blood [61,116]. For other instances, drug exposure measured in whole blood may only imperfectly reflect the actual *in vivo* exposure because of the confounding effect of erythrocytes/plasma drug distribution and its variability. Together with enzymatic systems present in erythrocytes and/or PBMCs that metabolize cytotoxic drugs, these are all processes likely to spuriously affect the analyte concentration measurements in plasma. For example, the enzyme dihydropyrimidine dehydrogenase (DPD) present in erythrocytes and PBMCs can prematurely degrade 5-fluorouracil [122]. Therefore, this may lead to spuriously low drug level in whole blood or derived plasma if not centrifuged immediately. On the other hand, the presence of key enzymes in blood formed elements can be exploited to perform pre-emptive genotyping or *ex vivo* phenotyping tests, prior to chemotherapies initiation. For 5-fluorouracil, DPD phenotyping and genotyping for the *DPYD* gene in PBMCs is strongly advised (mandatory in France [123]) for identifying patients with reduced DPD activity who are at risk of developing major toxicity [124,125]. Prior to treatment with thiopurine drugs, similar pre-emptive *ex vivo* phenotyping tests can be also performed in erythrocytes using LC-MS/MS [126,127] for identifying the patients with defect in thiopurine methyltransferase (TPMT) activity, who are therefore at risk to develop major toxicities.

Obtaining other biological fluids such as urine is much less invasive for the patients. Drugs and/or phase I and II metabolites thereof that are renally excreted are present at much higher levels in urine as compared to blood/plasma and analytical sensitivity is generally not an issue. Thus, urine sample preparation generally requires a simple dilution step and drug concentration can be normalized with creatinine levels measured in parallel or by specific gravity as commonly applied in drug doping testing [128]. However, while homeostasis tightly regulates plasma matrix composition, there is an important inter- and intra- individual variability in urine matrix that varies notably according to hydration status and renal function making it cumbersome to standardize. This is especially problematic for LC-MS/MS quantification in the absence of stable isotopically labelled IS of target analytes. Overall, drugs quantification in urine is only used for clinical research for pharmacokinetics studies and not for TDM.

Saliva constitutes another example of non-invasive biological matrix that can be rather easily collected for cytotoxic drugs analyses. For instance, methotrexate has been quantified in saliva to study its detrimental effect on tooth enamel for patients receiving high doses, and for assessing the potential relationship between saliva methotrexate levels and dental side-effects [58]. Because not all drugs are secreted in saliva, this biological fluid is not always suitable for analyses.

Finally, tears constitute a rather unusual matrix that has been used for TDM of cytotoxic drugs [53]. Ophthalmological issues are known to occur with several systemic anticancer chemotherapies [129]. An LC-MS/MS method has been developed for quantifying 5-fluorouracil and tegafur in tears showing a higher drug concentration at treatment initiation and a quick decrease of drug levels at termination [53].

Regarding samples preparation treatment, it usually involves plasma protein precipitation (44 % of the retrieved methods), liquid–liquid extraction (26 %), and solid phase extraction (22 %) among other less common techniques.

3.2.2. Liquid chromatography parameters

Prior to MS detection, samples are separated by LC in chromatographic methods lasting between 1.5 and 25 min and capable of separating up to 7 cytotoxic compounds simultaneously [112]. Undoubtedly, reverse-phase based high-performance liquid chromatography (HPLC) and ultra-high-performance liquid chromatography (UHPLC) columns have been mostly used for the separations of cytotoxic drugs and their metabolites: C18 mainly, but also C8 and C12 have been employed in more than 80 % of the methods reviewed, as listed in Table 1A and B. Less frequently and especially for polar compounds, amide- and amino-grafted columns have been used. Hydrophilic interaction liquid chromatography (HILIC) and anion exchange chromatography (AX) modes were also investigated in some articles [35,38,46,59,60]. To achieve different selectivity, columns with cyano- groups bound to the silica surface have also been used in a couple of articles [37,90]. Although most of the columns used and listed in this review are produced from bonded silica particles, it is interesting to note that other types of stationary phase are also used, such as porous graphitic carbon used in the quantification of tegafur and 5-fluorouracil in tears [53].

Analytical run time over the past 10 years has been markedly reduced in some instances from 20.3 min to less than 2 min notably thanks to progressive improvements in stationary phase composition, and also because of their increased separation performance and robustness leading to better selectivity and improved durability of LC columns [130]. The reduction in particle size improving peak efficiency has also been enabled by the introduction of UHPLC instruments, which can withstand higher pressures.

Additionally, it is worth mentioning that McTaggar et al [56] have developed a 1.5 min method for the determination of methotrexate in serum for patients undergoing chemotherapy. This rapid analysis time is achieved by the ingenious use of a 10 mm long pre-column instead of a conventional chromatography column [56]. Yet, caution should be exercised in general when considering very short analytical run to exclude the risk of co-elution of parent drug and any conjugated metabolite, such as demonstrated for the antiretroviral drug raltegravir and its glucuronide [131]: any co-elution would yield spuriously high levels of the parent drug, because of the in-source

dissociation of conjugated metabolite and conversion into the target analyte.

3.2.3. Mass spectrometry parameters

a) Internal standards

To reliably assess drug exposure in a patient, the LC-MS/MS strength relies on the dual specificity and selectivity based on both retention time and mass fragmentation of the compounds, associated with high sensitivity [12].

One of the critical points in the analyses of compounds in complex matrices by LC-MS/MS is the risk of matrix effects. Matrix effects are the suppressive or enhancing impact of matrix co-eluting compounds on the primary signal response of target analyte. Matrix effects are particularly detrimental to the accurate quantification of drugs in the complex biological matrices from patients. This effect can be reduced by using proper sample preparation and by adjusting LC conditions to avoid the coelution of problematic matrix components and analytes. Nevertheless, the use of stable isotopically labeled IS represents the most effective way to strengthen the LC-MS/MS technique by allowing compensation for variable matrix effect that adversely impacts the quantification. In theory, the same degree of ion suppression or enhancement should occur for the target analyte and its isotopically labeled (^{2}H,^{13}C, ^{15}N) analogue.

Remarkably, this review revealed that only 48 % of the retrieved methods developed for the quantification of cytotoxic agents by LC-MS/MS were using stable isotopically labelled IS of the target analytes (drug and metabolites). Those preferred IS were mostly found in methods for antimetabolites and their metabolites (i.e., 5-fluorouracil, capecitabine, cytarabine, decitabine, gemcitabine, thioguanine, methotrexate) (n = 24); mitotic inhibitors (paclitaxel, docetaxel, vinorelbine) (n = 7); alkylating agents and metabolites (busulfan, cyclophosphamide, melphalan, trabectedin, lurbinectedin) (n = 6); and miscellaneous latest generation agents (vorinostat, belinostat) (n = 6). Otherwise, related analogues of the target analytes have been used as IS in around 20 % of the methods (i.e., paclitaxel/docetaxel; vincristine/vinblastine/vinorelbine/vindoline; doxorubicin/daunorubicin; 5-fluorouracil/5-bromouracil/5-chlorouracil; methotrexate/aminopterin). In a few methods, structurally unrelated compounds have been used as IS: pioglitazone [108], fosfomycin [37], nicotinamide [54], theophylline [29], hexamethylphosphoramide [66]. Finally, in some methods such as the multiplexed assay developed by Derissen et al. (2015) [46], quantification relies on external calibration, except for a single compound for which the use of an IS was necessary, and the method was validated as such.

In the absence of stable isotopically labelled IS, the preparation of matrix-matched calibration samples might compensate for most of the plasma matrix effect, but not for its potential variability. Indeed, plasma composition from highly polymedicated cancer patients is likely to vary with respect to their complex fluctuating pathophysiological and clinical conditions (e.g., cachexia). Finally, the reliability of quantification of cytotoxic drugs in alternate biological matrices such as in patients' tissue specimens and tumor biopsies is questionable in the absence of labelled IS, given the difficulties, or impossibilities, to prepare matrix-matched calibrations.

Among the reviewed methods, there is the report of the use of a single labelled IS (e.g., methotrexate-d_3 [60]) for all other analytes contained in the same sample regardless of their respective chemical structures and retention times. Also, the use of "exotic" IS (i.e., compounds totally unrelated to the target analytes) can probably compensate for the analytical variability during sample preparation procedure (inaccuracy while pipetting, or inaccurate injection volume into the LC column (i.e., bubbles)), but it is not likely to compensate for matrix effect variability.

Yet, despite the many advantages, labeled IS are not devoid of limitations: restricted availability, as well as high, sometimes prohibitive costs, hamper their widespread use. Also, the use of isotopically labeled IS imposes several analytical precautions. In fact, labelled IS may not always fully compensate for the matrix effect, such as reported for the antimalarial drug piperaquine [132]. Subtle differences in physicochemical characteristics and lipophilicity may slightly influence the respective retention times of labelled and parent analytes. In case both compounds do not coelute in a region with erratic, distinctively different ion suppression pattern, the IS does not correct for the matrix effect at the analyte retention time, and this would in turn spuriously impact quantification. Also, beside the critical importance of IS isotopic purity, deuterium-labeled IS upon storage in solution may also slowly undergo proton exchange with water, leading to the progressive appearance of unlabeled compound in the IS solution, that would negatively impact accuracy for low drugs levels measurements.

b) Multiplexed analyses

The advantage of simultaneous quantification is the substantial analytical time, turnaround time (TAT) and costs reduction, by the establishment of common calibration curves. Moreover, the use of simplified and rapid extraction methods (i.e., plasma protein precipitation) followed by simultaneous quantification of cytotoxic drugs is most efficient for rapidly providing TDM results, including those for patients receiving combination chemotherapeutic regimens. For example, capecitabine and its metabolites has an analytical TAT of 10 min using this approach [34,133]. Overall, the technological improvements provided by LC-MS/MS both alleviate the laboratory staff workload and increase the analytical throughput which is a decisive aspect with regard to assay application in the clinical setting. LC-MS/MS allows responding without delay to analytical requests motivated by urgent medical needs and enables biomedical laboratories to provide medium to high-throughput analyses. The capacity of LC-MS/MS approaches to tackle the analyses of multiple compounds in a single analytical run is being widely exploited. Several multiplex LC-MS/MS methods (61 % of the methods) have been designed for quantifying either analogous compounds from a same therapeutic class (antimetabolites, taxanes, etc.) and their respective metabolites, or conversely, drugs part of the same cytotoxic combination regimens. Among the total of 90 published methods, 8 LC-MS/MS assays have been described for the simultaneous quantification of some, or the main, or all, components of frequently used cytotoxic combination regimens (CHOP, CAP, CTC, etc.) as detailed in Table 1B [63,108,110–114].

Some precautions with multiplexed analysis such as interference must be considered. As an example, compounds that have the same product or daughter ion are at higher risk or interference. Nevertheless, in this review, vorinostat and its glucuronide metabolite for example have been quantified in the same method using the same daughter ion [107] and the method still passed validation. This also applies to another example with vinorelbine and its deacetyl metabolite, also successfully validated [88].

c) Ionisation mode

As described in Tables 1A and 1B, all but one [84] methods that have been retrieved through the literature search detailed in Section 2 turn out to use electrospray ionization (ESI) as ionization mode. However, a careful reappraisal of the literature enabled to identify a few additional LC-MS/MS methods that used instead atmospheric pressure chemical ionization (APCI) for cytotoxic anticancer drugs quantification [134,135]. In general, APCI is appreciated because its is less vulnerable to matrix effect as compared to ESI [136], such as reported for the quantification of 5-fluorouracil in mouse plasma and tissues [137]. This was later confirmed by Montange et al. for capecitabine and its metabolites (5-fluorouracil, 5-DFCR and 5-DFUR) in human plasma

[138]. In their initial method development, these authors compared heat electrospray ionization (H-ESI) *versus* APCI, describing the latter as providing a better sensitivity with also less matrix effect [138]. Yet, the APCI mode for the quantification of antimetabolites remains exceptional, as evidenced in Table 1A and B whereby ESI was exclusively used, notably for this class of drugs without reporting any unacceptable impact on analytical performance [31–43,46–64].

In fact, APCI has been used for vinblastine quantification in a post-mortem case analysis [84], and also in canine plasma and urine [139]. Such approach was later questioned by van Heugen et al. who found a better sensitivity with ESI as compared to APCI for the quantification of vinorelbine and its metabolites in various matrices [90]. Overall, APCI and ESI have their respective advantages and limitations that depend on the molecules and the instruments used.

3.3. Biosafety precautions during cytotoxic samples bioanalyses

Guidelines have been issued for the biosafety precautions that are required during the manufacturing processes of pharmaceutical preparations of chemotherapies for patients. While the quantity of cytotoxic compounds that bioanalytical lab workers are at risk to be exposed is not within the same order of magnitude as compared to technicians who prepare the infusion pouches for chemotherapy administration, it is advised to adopt as a measure of precaution the same prudent procedures while handling these biohazardous substances, contained in stock, and working solutions, calibration samples and patient's biological materials.

Therefore, facilities equipped with class 2 biohazard hoods with air filtration dedicated for cytotoxics handling are necessary to minimize harmful levels of occupational exposure. Staff training, management of spill accidents, secured storage, use of adequate personal protective equipment (PPE), cleaning routines, waste disposal and safety cabinets maintenance as well as adequate ventilation systems, notably installed above the LC-MS/MS instrumentation are important points that need to be implemented in a laboratory handling such type of chemicals for TDM [140]. Methods to assess the contamination of work surfaces [141] and the exposure of laboratory staffs, especially in lower-income settings [142], exist and are essential when handling these highly toxic compounds.

3.4. Alternative analytical methods

Although LC-MS/MS constitutes the gold standard for TDM, several alternative methods have been developed for the TDM of selected cytotoxic drugs, notably for reducing the TAT to a minimum and avoiding the need of costly mass spectrometry instrumentations.

Immunoassays represent the most commonly used alternative to LC-MS/MS for the TDM of busulfan (nanoparticle-based immunoassay), methotrexate (Chemiluminescent Microparticle Immunoassay, CMIA), and for 5-fluorouracil. For instance, the my5FU assay requires a small sample volume, is amenable to procedure automatization reducing thereby the TAT and improving cost-effectiveness [143]. Nonetheless, because of their immunological principles, those assays unsurprisingly lack selectivity because of cross-reactions with for instance closely related metabolites. This leads to overestimation because of analytical cross-reactivity with metabolites. Notably, a cross-reaction is reported for 5-fluorouracil metabolites [122], and with 7-hydroxy-methotrexate for methotrexate [122,144].

Besides, recent biosensing technologies have been on the rise for possible TDM applications [16], with various detection methods, including optical (amongst the most widely spread method), mechanical, electrochemical, and even magnetic sensing [143]. Paclitaxel has been successfully quantified in serum as well as urine [145] using electrochemical biosensors and provides the proof of concept of feasibility. Yet, the clinical relevance of such measurement in urine remains to be determined, as the drug is majorly excreted through hepatic and biliary elimination. Finally, the electrochemical quantification of cyclophosphamide, etoposide, ifosfamide and ftorafur in serum with the possible detection of multiple compounds in one sample [146] opens the possibilities of multiplexed analyses, as exemplified by the selective simultaneous detection of both etoposide and methotrexate for sensors under development [147].

3.5. Clinical application of LC-MS/MS results for the TDM of cytotoxic drugs

While TDM is current practice in the field of infectious diseases treatments [148,149], for some immunosuppressive agents, particularly antirejection drugs, and in epileptology [11], its clinical use in oncology has been limited [150]. Methotrexate constitutes a notable exception in the context of leucovorin rescue, as well as busulfan and 5-fluorouracil, for which there has been an early recognition of their significant inter-individual PK variability and the importance of TDM-guided dosing adjustments [151]. Indeed, routine TDM implementation as compared to body weight (BW)– or Body Surface Area (BSA)-doses decisively improves clinical outcome for some chemotherapeutic drugs such as well demonstrated for busulfan [152–154].

Several strong arguments exist for justifying the TDM of cytotoxic drugs. First, there is a very high inter-individual PK variability for most of these cytotoxic drugs, and dose adjustment based on elementary prior factors such as BSA or BW is only loosely correlated to the drug clearance and overall does not account for the complex pathophysiological and clinical conditions of patients [10]. Also, there are no precocious PD markers of activity (such as in the case of coumaric anticoagulants and international normalised ratio (INR)) and, finally, PK-PD relationships have been established for many cytotoxic drugs [10]. Currently however, TDM for chemotherapeutic drugs is mostly motivated by suspected toxicity or in case of non-response, but very rarely as a systematic standard monitoring. As a result, most of the cytotoxic drugs are still poorly monitored and TDM is rarely implemented in clinical practice for the management of oncological patients, despite being advocated since decades [10,16].

The fact that not all hospital centers have access to mass spectrometry facilities, nor have a staff trained in TDM, hampers the wide implementation of TDM of cytotoxics in the clinical setting [16]. In addition, the safety requirements place a further burden on laboratories. Also, the prolonged intervals between doses administration, corresponding generally to the 21-day delay for bone marrow recovery, or because some cytotoxics are given as a one-time short-duration treatment, makes it logistically difficult to adjust drug dosage in real-time. This is further complexified since the exposure is typically assessed with the area under the drug concentration–time curve (AUC) [10] and not as a single-point concentration (peak (C_{max}) or trough (C_{min})), and inter-occasion variabilities between two dose makes the measure of exposure barely representative of the global exposure level of a patient [16]. Moreover, the targeted therapeutic ranges in oncology may vary depending on the malignancies and co-administered treatments, and the effect of the therapy is not readily assessable in most cases, contrary to antibiotic therapies for instance.

With regard to *a priori* cytotoxic drugs dosage selection, a notable exception to the rule of BW- or BSA-based dosing is carboplatin, for which the AUC-based dosage is used. This approach relies on the creatinine clearance, which strongly reflects the clearance of carboplatin: the desired carboplatin AUC exposure is attained by using glomerular filtration rate (GFR) as an indicator for prescribing the relevant dosage. This technique is frequently employed in adults but proves complicated to apply to pediatric patients, particularly infants and neonates, because obtaining dependable estimates of GFR is more challenging in this population [155]. The target AUC is well defined in this case: 7.8 mg•min/mL in adults and children, and 5.2 mg•min/mL in infants [155]. As mentioned earlier, the target AUC can vary depending on the malignancy: in this precise case, neuroblastoma patients may benefit from a higher tar-

get AUC of 16.4 mg•min/mL [156]. Considering the ability to perform *a priori* dosage adjustment based on GFR for adults and older children, TDM of carboplatin may not represent an essential addition to treatment management in such cases, but may still improve therapeutic outcomes in infant and neonates.

Table 2 gives examples of targets -when known- for the considered cytotoxic drugs. The target AUCs and concentrations are related to their clinical context, meaning that it may vary depending on the treatment regimen and the type of cancer.

For several cytotoxic drugs listed in Table 2, targets have, to the best of our knowledge, not yet been defined. Still, there are continuous research efforts at getting better and more secure use of cytotoxic drugs by increasing our understanding of the existing link between PK / pharmacogenetics / tumor genotypes, and the response (or

Table 2

Available targets for the presented cytotoxic drugs. Various cytotoxic chemotherapies have defined target concentrations, often expressed as AUC. The presented targets are mostly dependant on the clinical context. TDM: therapeutic drug monitoring, HSCT: hematopoietic stem cell transplantation, ASCT: allogenic stem cell transplantation, CTC: cyclophosphamide-thiotepa-carboplatin regimen, tCTC: tiny CTC meaning two-thirds of CTC regimen doses, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, C_{max}: maximum/peak concentration.

Compound	Targets	Clinical context	Reference
Alkylating agents			
Busulfan	Cumulative AUC 78–101 mg•h/L	HSCT conditioning regimen in the context of leukemia	Bartelink et al. (2016) [152]
Melphalan	AUC > 12.84 mg•h/L	ASCT in the context of myeloma	Nath et al. (2016) [157]
Cyclophosphamide	Carboxyethylphosphoramide mustard: AUC 300–350 μmol•h/L Hydroxycyclophosphamide: AUC > 50 μmol•h/L	HSCT conditioning regimen in the context of leukemia	Salinger et al. (2006) [158]
Thiotepa	CTC: sum of thiotepa and tepa AUC 47 μmol•h/L	Patients with high-risk primary breast cancer or advanced breast, germ cell or ovarian cancer; targets used to validate TDM strategy	Huitema et al. (2001) [159]
	tCTC: sum of thiotepa and tepa AUC 35 μmol•h/L		
Lurbinectedin	AUC 1000–1700 ng·h/L	SCLC	Fernandez-Teruel et al. (2022) [160]
Carboplatin	AUC over 3 days 5.2–7.8 mg•min/mL	Pediatric patients (incl. neonates and infants)	Barnett et al. (2023) [155]
	AUC over 3 days 24 mg•min/mL	Germ cell tumours, paclitaxel-ifosfamide-carboplatin-etoposide regimen	Motzer et al. (2000) [161]
	AUC 16.4 mg•min/mL	Pediatric neuroblastoma, carboplatin-etoposide-melphalan regimen	Duong et al. (2019) [156]
Anti-metabolites			
5-Fluorouracil	AUC 20–30 mg•h/L	Adjuvant or metastatic colorectal cancer	Lemaitre et al. (2018) [162]
Capecitabine	Not clearly defined for oral prodrugs of 5-fluorouracil		
Tegafur	Not clearly defined for oral prodrugs of 5-fluorouracil		
Methotrexate (high dose)	Maintain plasma concentration at 700–1000 μM over 1–6 h	Osteosarcoma	Nagamine et al. (2023) [163]
	Post-infusion TDM until methotrexate plasma levels reaches < 0.05 μM − 0.1 μM	Leucovorin rescue	Widemann et al. (2006) [164]
Thioguanine	Toxicity threshold of 6-thioguanine for myelotoxicity: 450 pmol/8 × 10^8 RBC	Inflammatory bowel disease in the context of azathioprine treatment	Gearry et al. (2005) [165]
Mercaptopurine	6-methylmercaptopurine nucleotides: <6000 pmol/8 × 10^8 RBC	Pediatric acute leukemia	de Beaumais et al. (2024) [166]
Pemetrexed	AUC 123–205 mg·h/L	NSCLC	de Rouw et al. (2019) [167]
Mitotic inhibitors			
Docetaxel	AUC 3.7–4.9 mg•h/L	Advanced solid tumours; targets used to validate TDM strategy	Engels et al. (2011) [168]
Paclitaxel	AUC 31.5–45 μM•h	Pediatric leukemia	Woo et al. (1999) [169]
	Plasma concentration > 0.05 μM for 26 to 31 h	Advanced NSCLC	Joerger et al. (2016) [170]
Cabazitaxel	Toxicity threshold for severe neutropenia (grade ≥ 3): plasma concentration > 4.96 ng/mL 6 h after the start of infusion	Data pooled from 5 clinical studies	Agema et al. (2023) [171]
Vincristine	AUC 50–100 μg•h/l	Neonates and infants	Barnett et al. (2022) [172]
Vinorelbine	C_{max} 1–2.7 ng/mL	Oral metronomic vinorelbine in association with dexamethasone in castration-resistant prostate cancer patients	Di Desidero et al. (2016) [89]
Eribulin	Median AUC associated with tumour shrinkage 785 ng•h/mL	Locally advanced or metastatic breast cancer	Majid et al. (2014) [173]
Topoisomerase inhibitors			
Etoposide	AUC > 254.8 mg•h/L	SCLC	Freyer et al. (2001) [174]
	AUC 4.6–8.2 mg•min/mL	Pediatric soft tissue sarcoma	Lowis et al. (1998) [175]
Other categories			
Vorinostat	C_{max} > 270 ng/mL	Pediatric patients, mostly brain tumours	van Tilburg et al. (2019) [176]

absence of response) and/or the toxicity elicited by drug treatment. For all these studies, TDM plays a critical role which is briefly highlighted thereafter.

In the case of trabectedin, pre-dose pharmaco-metabolomics may decrease inter-individual variability in PK [177]. Cytarabine dosage in high-dose regimen may be adjusted based on serum creatinine value, as the occurrence of drug-induced neurotoxicity is strongly linked to renal impairment [178], whereas reduced dosage administered once daily instead of twice daily also showed to reduce neurotoxic events [178]. PK-PD analyses have been attempted for decitabine dosage adjustment but still need some refinements [179]. For gemcitabine, although target concentrations are seemingly not available yet, sparse sampling methods provide reliable model-based PK predictions which may simplify the future application of TDM for this drug [180]. Occurrence of acute kidney injury correlates with high clofarabine AUC, prompting the need for further investigations to define the toxicity threshold [181]. In the case of doxorubicin, it has been reported that BW and body mass index (BMI) should be used as an *a priori* dosage adjustment factor to limit the inter-individual PK variability between overweight and normal weight patients [182]. Exposure-response/toxicity relationships have been suggested for daunorubicin and daunorubicinol, but this still needs to be validated for defining target therapeutic ranges [183,184]. Physiologically based PK data suggest that epirubicin PK may be affected by hepatic and renal UGT2B7 gene expression, plasma albumin concentration, age, BSA, GFR, hematocrit and sex [185]. As with gemcitabine, pirarubicin may benefit from sparse sampling for reliable PK estimations making TDM certainly feasible once target concentrations will have been defined [186]. Dose-banding approach is supported by clinical evidence for actinomycin-D (dactinomycin), as well as for busulfan, etoposide, cyclophosphamide, and carboplatin, and PK surveillance may be beneficial in this context [187]. Dose adjustment of vinblastine may be beneficial for low-exposure pediatric patients, without clear AUC-toxicity relationship yet [188]. For the metabolism of irinotecan, UGT1A1 polymorphism is associated with the incidence of neutropenia: pharmacogenomics or phenotyping, alongside TDM, may therefore help to prevent the occurrence of severe treatment toxicity [10). Genetic polymorphism is also affecting the metabolism of 5-azacytidine, such as highlighted in case reports of fatal toxicity or non-response, in case of poor, or rapid cytidine deaminase metabolism, respectively [189,190]. Furthermore, in a recent population pharmacokinetic (popPK) analysis, both C_{max} and steady-state AUC (AUC_{ss}) of 5-azacytidine were found to be predictors of relapse-free survival, and AUC_{ss} was also a predictor of overall survival [191]. Finally, although liver dysfunction is associated with elevated AUC, no exposure-toxicity relationship for belinostat has been yet established [192].

As the exposure is often assessed through the AUC, or even sometimes the C_{max}, LC-MS/MS methods need therefore to possess the suitable dynamic range to cover the entire range of plasma concentrations expected in patients, spanning from C_{max} to C_{min} levels. For example, for cyclophosphamide, the highest reported quantification limit is 40,000 ng/mL [114], a relatively high concentration as compared to that of other drugs, that would nonetheless still lie below the peak cyclophosphamide C_{max} of as high as 50,000 ng/mL that has been reported in patients [193]. Simultaneous quantification of both non-diluted and diluted samples at expected C_{max} may counteract this problem, if signal saturation or carryover is hindering the analysis at such high concentrations.

Numerous approaches exist for treatment individualization, including the test-dose methods as well as *a priori* and *a posteriori* approaches, which have been described in the context of dose fine-tuning of anticancer agents [194]. Pharmacogenomics, pharmacometabolomic and pathway phenotyping are tools that allow for *a priori* dosage adjustment, while TDM, by essence, allows to perform *a posteriori* dosage adjustment. These approaches can be all combined in the field of pharmacometrics in order to perform model-informed precision dosing (MIPD) [195]. popPK models are developed to identify relevant factors (i.e., covariates) that influence the drug PK. With such models, and knowing the patient's individual characteristics, *a priori* estimations of the drug PK in a specific case can be made. If TDM is also performed, these predictions can be refined through *a posteriori* Bayesian estimation. Moreover, popPK-PD models can be developed when response data are also available. The challenges of using efficacy biomarkers for PD-TDM in oncology have been thoroughly reviewed, which highlights their potential as key components in precision oncology [196]. Overall, the availability of pharmacometric models for cytotoxic drugs is far from scarce and, alongside analytical progress, will allow for a refined implementation of TDM through MIPD.

4. Conclusion, challenges, and future perspectives

Even in the era of targeted protein kinases inhibitors, monoclonal antibodies and immune checkpoint inhibitors [197], cytotoxic drugs still constitute an essential part of the current armamentarium against cancer. Even more at the present time, thanks to the availability of various drug combination regimens. The delicate equilibrium between drug administration, recovery period and drug combination has been progressively refined over the decades and has allowed to increase the rate of successful clinical responses. For instance, for the hematopoietic stem cell transplantation conditioning regimen with busulfan and cyclophosphamide, the order of drug administration has been demonstrated to impact treatment outcomes [198]. This is one of the many examples showing that cytotoxic chemotherapy can still be refined, going beyond dosage adjustment, and is meticulous in many aspects.

Still, in the growing movement of personalized medicine, there is a definite need to perform randomized controlled clinical trials for assessing whether TDM-guided dosing adjustments of cytotoxic drugs tailored to the individual patient would, as compared to mere BW- or BSA-adjusted dosing, improve clinical outcomes by optimizing treatment efficacy, reducing the risk of TRT, as well as avoiding the emergence of treatment resistance, and relapses [199]. Additionally, these improvements represent non-negligible milestones for the safe and effective use of cytotoxics in challenging populations such as in pediatrics patients [200].

To that end, the LC-MS/MS technology provides the possibility to accommodate multiplexed analyses with sensitivity, selectivity, and specificity in ever shorter run times, and is ideally suited for TDM analyses. Still, there is room for improvement, notably with a more systematic and general use of labelled IS, especially since there is now an increasing number of manufacturers that propose high quality stable isotopically labelled IS [201,202]. Also, standardization of method validation procedures is essential to ensure consistency across laboratories and would definitely benefit from external quality programs organized for a greater number of cytotoxic drugs, for extending the proficiency programs already available for methotrexate, busulfan [203], 5-fluorouracil [204], and more recently, thiopurines [205].

Despite many advantages, LC-MS/MS-based TDM for cytotoxic anticancer drugs faces several challenges that may limit its widespread adoption. In fact, it is rarely implemented in clinical practice due to a lack of analytical and clinical validation and harmonization, logistical constraints and, also, to some extent, reluctance from oncologists who still ask for the definitive demonstration of its clinical usefulness. In addition, implementation of these assays in clinical laboratories may require substantial analytical expertise and the needs of skilled laboratory technicians who can master the LC-MS/MS technology with instruments that are also costly, even though their price tends to democratize, and finally the need of expertise in clinical pharmacoki-

netics for TDM interpretation. To tackle some of the logistical and analytical constraints for the TDM of cytotoxics, innovative technologies may offer new perspectives for a possible facilitated access to the implementation of the TDM of cytotoxics [16]. In the meantime, the numerous LC-MS/MS methods that have been developed are currently invaluable in clinical research for increasing our knowledge on the real-life pharmacokinetics of those cytotoxic drugs in patients.

Funding

This work was supported by the Swiss National Science Foundation (SNF), grant number No 200021_207900/1.

CRediT authorship contribution statement

M. Briki: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **A. Murisier:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Supervision. **M. Guidi:** Conceptualization, Data curation, Project administration, Software, Supervision, Validation, Writing – review & editing. **C. Seydoux:** Conceptualization, Validation, Writing – review & editing. **T. Buclin:** Conceptualization, Funding acquisition, Project administration, Supervision. **C. Marzolini:** Data curation, Investigation, Supervision. **F.R. Girardin:** Supervision, Writing – review & editing. **Y. Thoma:** Funding acquisition, Software. **S. Carrara:** Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision. **E. Choong:** Data curation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **L.A. Decosterd:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] L. Falzone, S. Salomone, M. Libra, Evolution of cancer pharmacological treatments at the turn of the third millennium, Front. Pharmacol. 9 (2018).
[2] V.T. DeVita Jr., E. Chu, A history of cancer chemotherapy, Cancer Res. 68 (21) (2008) 8643–8653.
[3] M.D. Hellmann, B.T. Li, J.E. Chaft, M.G. Kris, Chemotherapy remains an essential element of personalized care for persons with lung cancers, Ann Oncol. 27 (10) (2016) 1829–1835.
[4] S.G. Rudd, Targeting pan-essential pathways in cancer with cytotoxic chemotherapy: challenges and opportunities, Cancer Chemother Pharmacol. 92 (4) (2023) 241–251.
[5] C. Bailly, X. Thuru, B. Quesnel, Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times, NAR Cancer. 2 (1) (2020).
[6] J. Sun, Q. Wei, Y. Zhou, J. Wang, Q. Liu, H. Xu, A systematic analysis of FDA-approved anticancer drugs, BMC Syst Biol. 11 (Suppl 5) (2017) 87.
[7] G.K. Rivera, D. Pinkel, J.V. Simone, M.L. Hancock, W.M. Crist, Treatment of acute lymphoblastic leukemia. 30 years' experience at St. Jude Children's Research Hospital, N Engl J Med. 329 (18) (1993) 1289–1295.
[8] NIH - National Cancer Institute [Available from: https://www.cancer.gov/research/progress/250-years-milestones.
[9] J.L. Marshall, Maximum-tolerated dose, optimum biologic dose, or optimum clinical value: dosing determination of cancer therapies, J Clin Oncol. 30 (23) (2012) 2815–2816.
[10] A. Paci, G. Veal, C. Bardin, D. Leveque, N. Widmer, J. Beijnen, et al, Review of therapeutic drug monitoring of anticancer drugs part 1–cytotoxics, Eur J Cancer. 50 (12) (2014) 2010–2019.
[11] N. Widmer, D. Werner, E. Grouzmann, C.B. Eap, O. Marchetti, A. Fayet, et al, Therapeutic drug monitoring: clinical practice, Rev Med Suisse. 4 (165) (2008).
[12] L.A. Decosterd, N. Widmer, P. Andre, M. Aouri, T. Buclin, The emerging role of multiplex tandem mass spectrometry analysis for therapeutic drug monitoring and personalized medicine, Trac-Trend Anal Chem. 84 (2016) 5–13.
[13] M.E. de Jonge, A.D. Huitema, J.H. Schellens, S. Rodenhuis, J.H. Beijnen, Individualised cancer chemotherapy: strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review, Clin Pharmacokinet. 44 (2) (2005) 147–173.
[14] Qutaiba Ahmad Al Khames Aga YAB, Hala Mousa Sbaih. Therapeutic Drug Monitoring of Cytotoxic Drugs. Annals of Tropical Medicine and Public Health. 2020;10(2).
[15] T. Buclin, Y. Thoma, N. Widmer, P. Andre, M. Guidi, C. Csajka, et al, The steps to therapeutic drug monitoring: A structured approach illustrated with imatinib, Front Pharmacol. 11 (2020) 177.
[16] M. Briki, P. Andre, Y. Thoma, N. Widmer, A.D. Wagner, L.A. Decosterd, et al, Precision oncology by point-of-care therapeutic drug monitoring and dosage adjustment of conventional cytotoxic chemotherapies: A perspective, Pharmaceutics. 15 (4) (2023).
[17] S. Kurbanoglu, N.K. Bakirhan, M. Gumustas, S.A. Ozkan, Modern assay techniques for cancer drugs: Electroanalytical and liquid chromatography methods, Crit Rev Anal Chem. 49 (4) (2019) 306–323.
[18] Y. Pashaei, M. Mehrabi, M. Shekarchi, A review on various analytical methods for determination of anthracyclines and their metabolites as anti-cancer chemotherapy drugs in different matrices over the last four decades, Trac-Trend Anal Chem. 130 (2020).
[19] R. Sabourian, S.Z. Mirjalili, N. Namini, F. Chavoshy, M. Hajimahmoodi, M. Safavi, HPLC methods for quantifying anticancer drugs in human samples: A systematic review, Anal Biochem. 610 (2020) 113891.
[20] F. Aucella, V. Lauriola, G. Vecchione, G.L. Tiscia, E. Grandone, Liquid chromatography-tandem mass spectrometry method as the golden standard for therapeutic drug monitoring in renal transplant, J Pharm Biomed Anal. 86 (2013) 123–126.
[21] R.L. Chen, L.H. Fang, X.Y. Yang, M. El Amrani, E.V. Uijtendaal, Y.F. Chen, et al, Therapeutic drug monitoring of busulfan in patients undergoing hematopoietic cell transplantation: A pilot single-center study in Taiwan, Pharmaceuticals (basel) 14 (7) (2021).
[22] F.A. de Castro, B.P. Simoes, A.L. Godoy, F.M. Bertagnoli Trigo, E.B. Coelho, V.L. Lanchote, Use of an oral busulfan test dose in patients undergoing hematopoietic stem cell transplantation treated with or without fludarabine, J Clin Pharmacol. 56 (12) (2016) 1555–1562.
[23] C. Ekhart, A. Gebretensae, H. Rosing, S. Rodenhuis, J.H. Beijnen, A.D. Huitema, Simultaneous quantification of cyclophosphamide and its active metabolite 4-hydroxycyclophosphamide in human plasma by high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (LC-MS/MS), J Chromatogr B Analyt Technol Biomed Life Sci. 854 (1–2) (2007) 345–349.
[24] Y. Harahap, A. Yanuar, C. Muhammad, M. Melhan, D.J. Purwanto, Quantification of 3-hydroxypropyl mercapturic acid in the urine of patients with breast cancer to monitor cyclophosphamide toxicity, Ther Drug Monit. 42 (4) (2020) 548–553.
[25] H. von Stedingk, H. Xie, T. Hatschek, T. Foukakis, A. Ryden, J. Bergh, et al, Validation of a novel procedure for quantification of the formation of phosphoramide mustard by individuals treated with cyclophosphamide, Cancer Chemother Pharmacol. 74 (3) (2014) 549–558.
[26] L. van Andel, H. Rosing, R. Lubomirov, P. Aviles, S. Fudio, M.M. Tibben, et al, Development and validation of a liquid chromatography-tandem mass spectrometry assay for the quantification of lurbinectedin in human plasma and urine, J Pharm Biomed Anal. 158 (2018) 160–165.
[27] G. Egerer, K. Eisenlohr, M. Gronkowski, J. Burhenne, K.D. Riedel, G. Mikus, The NK(1) receptor antagonist aprepitant does not alter the pharmacokinetics of high-dose melphalan chemotherapy in patients with multiple myeloma, Br J Clin Pharmacol. 70 (6) (2010) 903–907.
[28] I.D. Davies, J.P. Allanson, R.C. Causon, Rapid determination of the anti-cancer drug melphalan (Alkeran (TM)) in human serum and plasma by automated solid phase extraction and liquid chromatography tandem mass spectrometry, Chromatographia. 52 (2000) S92–S97.
[29] M.A. El Mubarak, E.K. Stylos, M.V. Chatziathanasiadou, C. Danika, G.A. Alexiou, P. Tsekeris, et al, Development and validation of simple step protein precipitation UHPLC-MS/MS methods for quantitation of temozolomide in cancer patient plasma samples, J Pharm Biomed Anal. 162 (2019) 164–170.
[30] E. Di Gregorio, G. Miolo, A. Steffan, G. Corona, Novel method for fast trabectedin quantification using hydrophilic interaction liquid chromatography and tandem mass spectrometry for human pharmacokinetic studies, J Pharm Biomed Anal. 185 (2020) 113261.
[31] M. Donnette, L. Osanno, M. Giocanti, G. Venton, L. Farnault, Y. Berda-Haddad, et al, Determination of 5-azacitidine in human plasma by LC-MS/MS: application to pharmacokinetics pilot study in MDS/AML patients, Cancer Chemother Pharmacol. 91 (3) (2023) 231–238.
[32] N.M. Anders, T.M. Wanjiku, P. He, N.S. Azad, M.A. Rudek, A robust and rapid liquid chromatography tandem mass spectrometric method for the quantitative analysis of 5-azacytidine, Biomed Chromatogr. 30 (3) (2016) 494–496.
[33] C.J. Wang, T. Li, P.P. Lin, Y. Tao, X. Jiang, X. Li, et al, Pharmacokinetic and safety comparison of two capecitabine tablets in patients with colorectal or breast cancer under fed conditions: A multicenter, randomized, open-label, three-period, and reference-replicated crossover study, Adv Ther. 38 (9) (2021) 4798–4814.
[34] P. Deng, C. Ji, X. Dai, D. Zhong, L. Ding, X. Chen, Simultaneous determination of capecitabine and its three nucleoside metabolites in human plasma by high performance liquid chromatography-tandem mass spectrometry, J Chromatogr B Analyt Technol Biomed Life Sci. 989 (2015) 71–79.
[35] M.J. Deenen, H. Rosing, M.J. Hillebrand, J.H. Schellens, J.H. Beijnen, Quantitative determination of capecitabine and its six metabolites in human plasma using liquid chromatography coupled to electrospray tandem mass

spectrometry, J Chromatogr B Analyt Technol Biomed Life Sci. 913–914 (2013) 30–40.
[36] B. Reigner, S. Clive, J. Cassidy, D. Jodrell, R. Schulz, T. Goggin, et al, Influence of the antacid Maalox on the pharmacokinetics of capecitabine in cancer patients, Cancer Chemother Pharmacol. 43 (4) (1999) 309–315.
[37] X. Tu, Y. Lu, D. Zhong, Y. Zhang, X. Chen, A sensitive LC-MS/MS method for quantifying clofarabine triphosphate concentrations in human peripheral blood mononuclear cells, J Chromatogr B Analyt Technol Biomed Life Sci. 964 (2014) 202–207.
[38] C. Abbara, G. Drevin, S. Ferec, S. Ghamrawi, S. Souchet, J.B. Robin, et al, Slower degradation rate of cytarabine in blood samples from acute myeloid leukemia by comparison with control samples, Cancer Chemother Pharmacol. 86 (5) (2020) 687–691.
[39] M. Donnette, C. Solas, M. Giocanti, G. Venton, L. Farnault, Y. Berda-Haddad, et al, Simultaneous determination of cytosine arabinoside and its metabolite uracil arabinoside in human plasma by LC-MS/MS: Application to pharmacokinetics-pharmacogenetics pilot study in AML patients, J Chromatogr B Analyt Technol Biomed Life Sci. 1126–1127 (2019) 121770.
[40] S. Chilakala, Y. Feng, L. Li, R. Mahfouz, E. Quteba, Y. Sauntharajah, et al, Tracking Decitabine Incorporation into Malignant Myeloid Cell DNA in vitro and in vivo by LC-MS/MS with Enzymatic Digestion, Sci Rep. 9 (1) (2019) 4558.
[41] J. Roosendaal, H. Rosing, L. Lucas, A. Oganesian, J.H.M. Schellens, J.H. Beijnen, Development, validation, and clinical application of a high-performance liquid chromatography-tandem mass spectrometry assay for the quantification of total intracellular beta-decitabine nucleotides and genomic DNA incorporated beta-decitabine and 5-methyl-2'-deoxycytidine, J Pharm Biomed Anal. 164 (2019) 16–26.
[42] H. Liu, Y. Liu, T. Zhou, P. Zhou, J. Li, A. Deng, Ultrasensitive and specific detection of anticancer drug 5-fluorouracil in blood samples by a surface-enhanced raman scattering (SERS)-based lateral flow immunochromatographic assay, Molecules. 27 (13) (2022).
[43] M. Oman, Y. Wettergren, E. Odin, S. Westermark, P. Naredi, O. Hemmingsson, et al, Pharmacokinetics of preoperative intraperitoneal 5-FU in patients with pancreatic ductal adenocarcinoma, Cancer Chemother Pharmacol. 88 (4) (2021) 619–631.
[44] A. Varma, M. Jayanthi, B. Dubashi, D.G. Shewade, R. Sundaram, Genetic influence of DPYD*9A polymorphism on plasma levels of 5-fluorouracil and subsequent toxicity after oral administration of capecitabine in colorectal cancer patients of South Indian origin, Drug Metab Pers Ther. 35 (4) (2020).
[45] Y. Ju, Y. Zhou, Y. Peng, J. Wu, C. Zhang, W. Guo, et al, Establishment and clinical application of liquid chromatography-tandem mass spectrometric method for simultaneous determination of plasma 5-fluorouracil, Zhonghua Yi Xue Za Zhi. 96 (10) (2016) 817–821.
[46] E.J. Derissen, M.J. Hillebrand, H. Rosing, J.H. Schellens, J.H. Beijnen, Development of an LC-MS/MS assay for the quantitative determination of the intracellular 5-fluorouracil nucleotides responsible for the anticancer effect of 5-fluorouracil, J Pharm Biomed Anal. 110 (2015) 58–66.
[47] B. Buchel, P. Rhyn, S. Schurch, C. Buhr, U. Amstutz, C.R. Largiader, LC-MS/MS method for simultaneous analysis of uracil, 5,6-dihydrouracil, 5-fluorouracil and 5-fluoro-5,6-dihydrouracil in human plasma for therapeutic drug monitoring and toxicity prediction in cancer patients, Biomed Chromatogr. 27 (1) (2013) 7–16.
[48] C.J. Peer, T.J. McManus, H.I. Hurwitz, W.P. Petros, Development and utilization of a combined LC-UV and LC-MS/MS method for the simultaneous analysis of tegafur and 5-fluorouracil in human plasma to support a phase I clinical study of oral UFT(R)/leucovorin, J Chromatogr B Analyt Technol Biomed Life Sci. 898 (2012) 32–37.
[49] M.A. Serdar, E. Sertoglu, M. Uyanik, S. Tapan, O. Akin, M. Cihan, Determination of 5-fluorouracil and dihydrofluorouracil levels by using a liquid chromatography-tandem mass spectrometry method for evaluation of dihydropyrimidine dehydrogenase enzyme activity, Cancer Chemother Pharmacol. 68 (2) (2011) 525–529.
[50] J.E. Kosovec, M.J. Egorin, S. Gjurich, J.H. Beumer, Quantitation of 5-fluorouracil (5-FU) in human plasma by liquid chromatography/electrospray ionization tandem mass spectrometry, Rapid Commun Mass Spectrom. 22 (2) (2008) 224–230.
[51] T. Bjanes, T. Kamceva, T. Eide, B. Riedel, J. Schjott, A. Svardal, Preanalytical stability of gemcitabine and its metabolite 2', 2'-Difluoro-2'-deoxyuridine in whole blood-assessed by liquid chromatography tandem mass spectrometry, J Pharm Sci. 104 (12) (2015) 4427–4432.
[52] C. Bowen, S. Wang, H. Licea-Perez, Development of a sensitive and selective LC-MS/MS method for simultaneous determination of gemcitabine and 2,2-difluoro-2-deoxyuridine in human plasma, J Chromatogr B Analyt Technol Biomed Life Sci. 877 (22) (2009) 2123–2129.
[53] R. Kuriki, T. Hata, K. Nakayama, Y. Ito, K. Misawa, S. Ito, et al, Tegafur and 5-fluorouracil levels in tears and changes in tear volume in long-term users of the oral anticancer drug S-1, Nagoya J Med Sci. 81 (3) (2019) 415–425.
[54] Z.X. Zhuang, H. Zhu, J. Wang, M.G. Zhu, H. Wang, W.Y. Pu, et al, Pharmacokinetic evaluation of novel oral fluorouracil antitumor drug S-1 in Chinese cancer patients, Acta Pharmacol Sin. 34 (4) (2013) 570–580.
[55] K. Hansson, H. Orrling, A. Blomgren, A. Isaksson, G. Schliamser, J. Heldrup, et al, Simultaneous determination of folate and methotrexate metabolites in serum by LC-MS/MS during high-dose methotrexate therapy, J Chromatogr B Analyt Technol Biomed Life Sci. 1186 (2021) 123007.
[56] M.P. McTaggart, B.G. Keevil, A rapid LC-MS/MS assay for the measurement of serum methotrexate in patients who have received high doses for chemotherapy, Ann Clin Biochem. 58 (6) (2021) 599–604.
[57] E. den Boer, R.J. Meesters, B.D. van Zelst, T.M. Luider, J.M. Hazes, S.G. Heil, et al, Measuring methotrexate polyglutamates in red blood cells: a new LC-MS/MS-based method, Anal Bioanal Chem. 405 (5) (2013) 1673–1681.
[58] I. Rodin, A. Braun, A. Stavrianidi, O. Shpigun, A validated LC-MS/MS method for rapid determination of methotrexate in human saliva and its application to an excretion evaluation study, J Chromatogr B Analyt Technol Biomed Life Sci. 937 (2013) 1–6.
[59] S.S. Zhao, M.A. Bichelberger, D.Y. Colin, R. Robitaille, J.N. Pelletier, J.F. Masson, Monitoring methotrexate in clinical samples from cancer patients during chemotherapy with a LSPR-based competitive sensor, Analyst. 137 (20) (2012) 4742–4750.
[60] J. Han, J. Xu, N. Sun, S. Jin, D. Mei, X. Wang, et al, Analysis of mono-, di-, and triphosphates of thioguanosine and methylthioinosine in children with acute lymphoblastic leukemia by LC-MS/MS, J Pharm Biomed Anal. 217 (2022) 114813.
[61] S.Y. Moon, J.H. Lim, E.H. Kim, Y. Nam, K.S. Yu, K.T. Hong, et al, Quantification of thiopurine nucleotides in erythrocytes and clinical application to pediatric acute lymphoblastic leukemia, Ther Drug Monit. 41 (1) (2019) 75–85.
[62] O.A. Attallah, M.A. Al-Ghobashy, A.T. Ayoub, M. Nebsen, Magnetic molecularly imprinted polymer nanoparticles for simultaneous extraction and determination of 6-mercaptopurine and its active metabolite thioguanine in human plasma, J Chromatogr A. 1561 (2018) 28–38.
[63] M.A. Al-Ghobashy, S.A. Hassan, D.H. Abdelaziz, N.M. Elhosseiny, N.A. Sabry, A.S. Attia, et al, Development and validation of LC-MS/MS assay for the simultaneous determination of methotrexate, 6-mercaptopurine and its active metabolite 6-thioguanine in plasma of children with acute lymphoblastic leukemia: Correlation with genetic polymorphism, J Chromatogr B Analyt Technol Biomed Life Sci. 1038 (2016) 88–94.
[64] S.A. Coulthard, P. Berry, S. McGarrity, A. Ansari, C.P.F. Redfern, Liquid chromatography-mass spectrometry for measuring deoxythioguanosine in DNA from thiopurine-treated patients, J Chromatogr B Analyt Technol Biomed Life Sci. 1028 (2016) 175–180.
[65] M.L. Oliveira, A. Rocha, G.H.B. Nardotto, L.F. Pippa, B.P. Simoes, V.L. Lanchote, Analysis of daunorubicin and its metabolite daunorubicinol in plasma and urine with application in the evaluation of total, renal and metabolic formation clearances in patients with acute myeloid leukemia, J Pharm Biomed Anal. 191 (2020) 113576.
[66] Y. Harahap, P. Ardiningsih, A. Corintias Winarti, D.J. Purwanto, Analysis of the doxorubicin and doxorubicinol in the plasma of breast cancer patients for monitoring the toxicity of doxorubicin, Drug Des Devel Ther. 14 (2020) 3469–3475.
[67] L.F. Pippa, M.L. Oliveira, A. Rocha, J.M. de Andrade, V.L. Lanchote, Total, renal and hepatic clearances of doxorubicin and formation clearance of doxorubicinol in patients with breast cancer: Estimation of doxorubicin hepatic extraction ratio, J Pharm Biomed Anal. 185 (2020) 113231.
[68] R.X. Yang, H.X. Ren, L. Zhuang, C.L. Gao, C. Dong, C.X. Luo, et al, Pharmacokinetic and myocardial enzyme profiles of two administration routes of epirubicin in breast cancer patients, Arzneimittelforschung. 62 (12) (2012) 677–681.
[69] C. Sottani, E. Leoni, B. Porro, B. Montagna, A. Amatu, F. Sottotetti, et al, Validation of an LC-MS/MS method for the determination of epirubicin in human serum of patients undergoing drug eluting microsphere-transarterial chemoembolization (DEM-TACE), J Chromatogr B Analyt Technol Biomed Life Sci. 877 (29) (2009) 3543–3548.
[70] P. de Bruijn, A.J. de Graan, A. Nieuweboer, R.H. Mathijssen, M.H. Lam, R. de Wit, et al, Quantification of cabazitaxel in human plasma by liquid chromatography/triple-quadrupole mass spectrometry: a practical solution for non-specific binding, J Pharm Biomed Anal. 59 (2012) 117–122.
[71] O. Maliszewska, A. Roszkowska, M. Lipinski, N. Treder, I. Oledzka, P. Kowalski, et al, Profiling docetaxel in plasma and urine samples from a pediatric cancer patient using ultrasound-assisted dispersive liquid-liquid microextraction combined with LC-MS/MS, Pharmaceutics. 15 (4) (2023).
[72] M.A.C. Vermunt, M. van Nuland, L.T. van der Heijden, H. Rosing, J.H. Beijnen, A. M. Bergman, Comparison of docetaxel pharmacokinetics between castration-resistant and hormone-sensitive metastatic prostate cancer patients, Cancer Chemother Pharmacol. 89 (6) (2022) 785–793.
[73] J.J. Hendrikx, A.C. Dubbelman, H. Rosing, A.H. Schinkel, J.H. Schellens, J.H. Beijnen, Quantification of docetaxel and its metabolites in human plasma by liquid chromatography/tandem mass spectrometry, Rapid Commun Mass Spectrom. 27 (17) (2013) 1925–1934.
[74] J.J. Hendrikx, M.J. Hillebrand, B. Thijssen, H. Rosing, A.H. Schinkel, J.H. Schellens, et al, A sensitive combined assay for the quantification of paclitaxel, docetaxel and ritonavir in human plasma using liquid chromatography coupled with tandem mass spectrometry, J Chromatogr B Analyt Technol Biomed Life Sci. 879 (28) (2011) 2984–2990.
[75] Jones JD, J. . LC-MS/MS Method for the Determination of Docetaxel in Human Serum for Clinical Research Thermo Scientific; 2012 [Available from: http://apps.thermoscientific.com/media/cmd/sola-spe/docetaxel_in_human_serum.pdf.
[76] J. Yang, X. Li, W. Li, X. Xi, Q. Du, F. Pan, et al, An improved LC-MS/MS method for determination of docetaxel and its application to population pharmacokinetic study in Chinese cancer patients, Biomed Chromatogr. 34 (8) (2020) e4857.
[77] S. Gao, J. Zhou, F. Zhang, H. Miao, Y. Yun, J. Feng, et al, Rapid and sensitive liquid chromatography coupled with electrospray ionization tandem mass spectrometry method for the analysis of paclitaxel, docetaxel, vinblastine, and vinorelbine in human plasma, Ther Drug Monit. 36 (3) (2014) 394–400.

[78] J. Guitton, S. Cohen, B. Tranchand, B. Vignal, J.P. Droz, M. Guillaumont, et al, Quantification of docetaxel and its main metabolites in human plasma by liquid chromatography/tandem mass spectrometry, Rapid Commun Mass Spectrom. 19 (17) (2005) 2419–2426.
[79] R.J. Morgan, T.W. Synold, J.A. Longmate, D.I. Quinn, D. Gandara, H.J. Lenz, et al, Pharmacodynamics (PD) and pharmacokinetics (PK) of E7389 (eribulin, halichondrin B analog) during a phase I trial in patients with advanced solid tumors: a California cancer consortium trial, Cancer Chemother Pharmacol. 76 (5) (2015) 897–907.
[80] S.M. Christner, R.A. Parise, P.S. Ivy, H. Tawbi, E. Chu, J.H. Beumer, Quantitation of paclitaxel, and its 6-alpha-OH and 3-para-OH metabolites in human plasma by LC-MS/MS, J Pharm Biomed Anal. 172 (2019) 26–32.
[81] M.A. Fernandez-Peralbo, F. Priego-Capote, M.D. Luque de Castro, A. Casado-Adam, A. Arjona-Sanchez, F.C. Munoz-Casares, LC-MS/MS quantitative analysis of paclitaxel and its major metabolites in serum, plasma and tissue from women with ovarian cancer after intraperitoneal chemotherapy, J Pharm Biomed Anal. 91 (2014) 131–137.
[82] J.B. Bulitta, P. Zhao, R.D. Arnold, D.R. Kessler, R. Daifuku, J. Pratt, et al, Mechanistic population pharmacokinetics of total and unbound paclitaxel for a new nanodroplet formulation versus Taxol in cancer patients, Cancer Chemother Pharmacol. 63 (6) (2009) 1049–1063.
[83] J.B. Bulitta, P. Zhao, R.D. Arnold, D.R. Kessler, R. Daifuku, J. Pratt, et al, Multiple-pool cell lifespan models for neutropenia to assess the population pharmacodynamics of unbound paclitaxel from two formulations in cancer patients, Cancer Chemother Pharmacol. 63 (6) (2009) 1035–1048.
[84] M. Klys, T. Konopka, M. Scislowski, P. Kowalski, Fatality involving vinblastine overdose as a result of a complex medical error, Cancer Chemother Pharmacol. 59 (1) (2007) 89–95.
[85] L.T. van der Heijden, A. Uittenboogaard, A.L. Nijstad, A. Gebretensae, G.J.L. Kaspers, J.H. Beijnen, et al, A sensitive liquid chromatographic-mass spectrometry method for the quantification of vincristine in whole blood collected with volumetric absorptive microsampling, J Pharm Biomed Anal. 225 (2023) 115232.
[86] Z. Yan, Z.L. Zhu, Z.Z. Qian, G. Hu, H.Q. Wang, W.H. Liu, et al, Pharmacokinetic characteristics of vincristine sulfate liposomes in patients with advanced solid tumors, Acta Pharmacol Sin. 33 (6) (2012) 852–858.
[87] R. Guilhaumou, C. Solas, A. Rome, M. Giocanti, N. Andre, B. Lacarelle, Validation of an electrospray ionization LC/MS/MS method for quantitative analysis of vincristine in human plasma samples, J Chromatogr B Analyt Technol Biomed Life Sci. 878 (3–4) (2010) 423–427.
[88] G. Corona, M. Gusella, A. Gaspardo, G. Miolo, L. Bertolaso, E. Pezzolo, et al, Rapid LC-MS/MS method for quantification of vinorelbine and 4-O-deacetylvinorelbine in human whole blood suitable to monitoring oral metronomic anticancer therapy, Biomed Chromatogr. (2018).
[89] T. Di Desidero, L. Derosa, L. Galli, P. Orlandi, A. Fontana, A. Fioravanti, et al, Clinical, pharmacodynamic and pharmacokinetic results of a prospective phase II study on oral metronomic vinorelbine and dexamethasone in castration-resistant prostate cancer patients, Invest New Drugs. 34 (6) (2016) 760–770.
[90] J.C. Van Heugen, J. De Graeve, G. Zorza, C. Puozzo, New sensitive liquid chromatography method coupled with tandem mass spectrometric detection for the clinical analysis of vinorelbine and its metabolites in blood, plasma, urine and faeces, J Chromatogr A. 926 (1) (2001) 11–20.
[91] C. Atasilp, P. Chansriwong, E. Sirachainan, T. Reungwetwattana, A. Puangpetch, S. Prommas, et al, Determination of irinotecan, SN-38 and SN-38 glucuronide using HPLC/MS/MS: Application in a clinical pharmacokinetic and personalized medicine in colorectal cancer patients, J Clin Lab Anal. 32 (1) (2018).
[92] E. Calandra, B. Posocco, S. Crotti, E. Marangon, L. Giodini, D. Nitti, et al, Cross-validation of a mass spectrometric-based method for the therapeutic drug monitoring of irinotecan: implementation of matrix-assisted laser desorption/ionization mass spectrometry in pharmacokinetic measurements, Anal Bioanal Chem. 408 (19) (2016) 5369–5377.
[93] E. Marangon, B. Posocco, E. Mazzega, G. Toffoli, Development and validation of a high-performance liquid chromatography-tandem mass spectrometry method for the simultaneous determination of irinotecan and its main metabolites in human plasma and its application in a clinical pharmacokinetic study, PLoS One. 10 (2) (2015) e0118194.
[94] P. Herviou, D. Richard, L. Roche, J. Pinguet, F. Libert, A. Eschalier, et al, Determination of irinotecan and SN38 in human plasma by TurboFlow liquid chromatography-tandem mass spectrometry, J Pharm Biomed Anal. 118 (2016) 284–291.
[95] M. Ramesh, P. Ahlawat, N.R. Srinivas, Irinotecan and its active metabolite, SN-38: review of bioanalytical methods and recent update from clinical pharmacology perspectives, Biomed Chromatogr. 24 (1) (2010) 104–123.
[96] F. D'Esposito, B.N. Tattam, I. Ramzan, M. Murray, A liquid chromatography/electrospray ionization mass spectrometry (LC-MS/MS) assay for the determination of irinotecan (CPT-11) and its two major metabolites in human liver microsomal incubations and human plasma samples, J Chromatogr B Analyt Technol Biomed Life Sci. 875 (2) (2008) 522–530.
[97] S. Khan, A. Ahmad, I. Ahmad, A sensitive and rapid liquid chromatography tandem mass spectrometry method for quantitative determination of 7-ethyl-10-hydroxycamptothecin (SN-38) in human plasma containing liposome-based SN-38 (LE-SN38), Biomed Chromatogr. 17 (8) (2003) 493–499.
[98] J.M. Janssen, N. de Vries, N. Venekamp, H. Rosing, A.D.R. Huitema, J.H. Beijnen, Development and validation of a liquid chromatography-tandem mass spectrometry assay for nine oral anticancer drugs in human plasma, J Pharm Biomed Anal. 174 (2019) 561–566.
[99] J. Burhenne, L. Liu, C.E. Heilig, A.D. Meid, M. Leisen, T. Schmitt, et al, Intracellular vorinostat accumulation and its relationship to histone deacetylase activity in soft tissue sarcoma patients, Cancer Chemother Pharmacol. 80 (2) (2017) 433–439.
[100] L. Liu, J.C. Detering, T. Milde, W.E. Haefeli, O. Witt, J. Burhenne, Quantification of vorinostat and its main metabolites in plasma and intracellular vorinostat in PBMCs by liquid chromatography coupled to tandem mass spectrometry and its relation to histone deacetylase activity in human blood, J Chromatogr B Analyt Technol Biomed Life Sci. 964 (2014) 212–221.
[101] P.S. Suresh, V.C. Devaraj, N.R. Srinivas, R. Mullangi, Review of bioanalytical assays for the quantitation of various HDAC inhibitors such as vorinostat, belinostat, panobinostat, romidepsin and chidamine, Biomed Chromatogr. 31 (1) (2017).
[102] R. Gu, T. Liu, X. Zhu, H. Gan, Z. Wu, J. Li, et al, Development and validation of a sensitive HPLC-MS/MS method for determination of chidamide (epidaza), a new benzamide class of selective histone deacetylase inhibitor, in human plasma and its clinical application, J Chromatogr B Analyt Technol Biomed Life Sci. 1000 (2015) 181–186.
[103] B.F. Kiesel, R.A. Parise, J. Tjornelund, M.K. Christensen, E. Loza, H. Tawbi, et al, LC-MS/MS assay for the quantitation of the HDAC inhibitor belinostat and five major metabolites in human plasma, J Pharm Biomed Anal. 81–82 (2013) 89–98.
[104] L.Z. Wang, D. Chan, W. Yeo, S.C. Wan, S. Chan, A. Chan, et al, A sensitive and specific liquid chromatography-tandem mass spectrometric method for determination of belinostat in plasma from liver cancer patients, J Chromatogr B Analyt Technol Biomed Life Sci. 878 (26) (2010) 2409–2414.
[105] K. Patel, S.M. Guichard, D.I. Jodrell, Simultaneous determination of decitabine and vorinostat (Suberoylanalide hydroxamic acid, SAHA) by liquid chromatography tandem mass spectrometry for clinical studies, J Chromatogr B Analyt Technol Biomed Life Sci. 863 (1) (2008) 19–25.
[106] R.A. Parise, J.L. Holleran, J.H. Beumer, S. Ramalingam, M.J. Egorin, A liquid chromatography-electrospray ionization tandem mass spectrometric assay for quantitation of the histone deacetylase inhibitor, vorinostat (suberoylanilide hydroxamicacid, SAHA), and its metabolites in human serum, J Chromatogr B Analyt Technol Biomed Life Sci. 840 (2) (2006) 108–115.
[107] L. Du, D.G. Musson, A.Q. Wang, High turbulence liquid chromatography online extraction and tandem mass spectrometry for the simultaneous determination of suberoylanilide hydroxamic acid and its two metabolites in human serum, Rapid Commun Mass Spectrom. 19 (13) (2005) 1779–1787.
[108] P. Qi, P. Li, L. Qiao, H. Xue, Y. Ma, S. Wei, et al, Simultaneous quantification of pirarubicin, doxorubicin, cyclophosphamide, and vincristine in human plasma of patients with non-Hodgkin's lymphoma by LC-MS/MS method, J Chromatogr B Analyt Technol Biomed Life Sci. 1224 (2023) 123754.
[109] K. Schmiegelow, S.N. Nielsen, T.L. Frandsen, J. Nersting, Mercaptopurine/Methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction, J Pediatr Hematol Oncol. 36 (7) (2014) 503–517.
[110] C. Shu, T. Zeng, S. Gao, T. Xia, L. Huang, F. Zhang, et al, LC-MS/MS method for simultaneous determination of thalidomide, lenalidomide, cyclophosphamide, bortezomib, dexamethasone and adriamycin in serum of multiple myeloma patients, J Chromatogr B Analyt Technol Biomed Life Sci. 1028 (2016) 111–119.
[111] J.J. Lee, J. Seraj, K. Yoshida, H. Mizuguchi, S. Strychor, J. Fiejdasz, et al, Human mass balance study of TAS-102 using (14)C analyzed by accelerator mass spectrometry, Cancer Chemother Pharmacol. 77 (3) (2016) 515–526.
[112] J. Zhou, S. Gao, F. Zhang, B. Jiang, Q. Zhan, F. Cai, et al, Liquid chromatography-tandem mass spectrometry method for simultaneous determination of seven commonly used anticancer drugs in human plasma, J Chromatogr B Analyt Technol Biomed Life Sci. 906 (2012) 1–8.
[113] J.M. Skolnik, J.S. Barrett, H. Shi, P.C. Adamson, A liquid chromatography-tandem mass spectrometry method for the simultaneous quantification of actinomycin-D and vincristine in children with cancer, Cancer Chemother Pharmacol. 57 (4) (2006) 458–464.
[114] M.E. de Jonge, S.M. van Dam, M.J. Hillebrand, H. Rosing, A.D. Huitema, S. Rodenhuis, et al, Simultaneous quantification of cyclophosphamide, 4-hydroxycyclophosphamide, N, N', N"-triethylenethiophosphoramide (thiotepa) and N, N', N"-triethylenephosphoramide (tepa) in human plasma by high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry, J Mass Spectrom. 39 (3) (2004) 262–271.
[115] N.B. Andriguetti, R.Z. Hahn, L.F. Lizot, S. Raymundo, J.L. Costa, K.F. da Cunha, et al, Analytical and clinical validation of a dried blood spot assay for the determination of paclitaxel using high-performance liquid chromatography-tandem mass spectrometry, Clin Biochem. 54 (2018) 123–130.
[116] R.N. Xu, J. Polzin, M. Kranz, P. Vaca, M. Metchkarova, M.J. Rieser, et al, Strategies for Developing Sensitive and Automated LC-MS/MS Assays of a Pharmaceutical Compound and Its Metabolite from Whole Blood Matrix, Pharmaceutics. 2 (2) (2010) 159–170.
[117] Teva Pharma AG, Doxorubicin-Teva® SwissMedicInfo [Available from: https://swissmedicinfo.ch/showText.aspx?textType=FI&lang=FR&authNr=59350.
[118] J. Blanc Mettral, N. Faller, S. Cruchon, L. Sottas, T. Buclin, L. Schild, et al, Imatinib uptake into cells is not mediated by organsic cation transporters OCT1, OCT2, or OCT3, but is influenced by extracellular pH, Drug Metab Lett. 13 (2019) 102–110.
[119] C. Marzolini, E. Paus, T. Buclin, R.B. Kim, Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance, Clin Pharmacol Ther. 75 (1) (2004) 13–33.
[120] E.S. Kim, J.J. Lee, G. He, C.W. Chow, J. Fujimoto, N. Kalhor, et al, Tissue platinum concentration and tumor response in non-small-cell lung cancer, J Clin Oncol. 30 (27) (2012) 3345–3352.

[121] S. Urien, F. Bree, F. Breillout, G. Bastian, A. Krikorian, J.P. Tillement, Vinorelbine high-affinity binding to human platelets and lymphocytes: distribution in human blood, Cancer Chemother Pharmacol. 32 (3) (1993) 231–234.
[122] Smita P, Narayan PA, J K, Gaurav P. Therapeutic drug monitoring for cytotoxic anticancer drugs: Principles and evidence-based practices. Front Oncol. 2022;12:1015200.
[123] [Available from: https://www.has-sante.fr/upload/docs/application/pdf/2018-12/recherche_dun_deficit_en_dihydropyrimidine_deshydrogenase_visant_a_prevenir_certaines_toxicites_severes_associees_aux_traite.pdf.
[124] M.A. Loriot, J. Ciccolini, F. Thomas, C. Barin-Le-Guellec, B. Royer, G. Milano, et al, Dihydropyrimidine dehydrogenase (DPD) deficiency screening and securing of fluoropyrimidine-based chemotherapies: Update and recommendations of the French GPCO-Unicancer and RNPGx networks, Bull Cancer. 105 (4) (2018) 397–407.
[125] J. Santini, G. Milano, A. Thyss, N. Renee, P. Viens, P. Ayela, et al, 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer, Br J Cancer. 59 (2) (1989) 287–290.
[126] L. Lennard, H.J. Singleton, High-performance liquid chromatographic assay of human red blood cell thiopurine methyltransferase activity, J Chromatogr B Biomed Appl. 661 (1) (1994) 25–33.
[127] L. Lennard, Implementation of TPMT testing, Br J Clin Pharmacol. 77 (4) (2014) 704–714.
[128] E.J. Cone, Y.H. Caplan, F. Moser, T. Robert, M.K. Shelby, D.L. Black, Normalization of urinary drug concentrations with specific gravity and creatinine, J Anal Toxicol. 33 (1) (2009) 1–7.
[129] A.E. Omoti, C.E. Omoti, Ocular toxicity of systemic anticancer chemotherapy, Pharm Pract (granada). 4 (2) (2006) 55–59.
[130] H. Rusli, R.M. Putri, A. Alni, Recent Developments of Liquid Chromatography Stationary Phases for Compound Separation: From Proteins to Small Organic Compounds, Molecules. (2022) 27(3).
[131] J.F. Jourdil, M. Bartoli, F. Stanke-Labesque, Lack of specificity for the analysis of raltegravir using online sample clean-up liquid chromatography-electrospray tandem mass spectrometry, J Chromatogr B Analyt Technol Biomed Life Sci. 877 (29) (2009) 3734–3738.
[132] N. Lindegardh, A. Annerberg, N.J. White, N.P. Day, Development and validation of a liquid chromatographic-tandem mass spectrometric method for determination of piperaquine in plasma stable isotope labeled internal standard does not always compensate for matrix effects, J Chromatogr B Analyt Technol Biomed Life Sci. 862 (1–2) (2008) 227–236.
[133] E.J. Derissen, B.A. Jacobs, A.D. Huitema, H. Rosing, J.H. Schellens, J.H. Beijnen, Exploring the intracellular pharmacokinetics of the 5-fluorouracil nucleotides during capecitabine treatment, Br J Clin Pharmacol. 81 (5) (2016) 949–957.
[134] G.P. Tamilarasi, K. Manikandan, V.R. Solomon, Liquid chromatography-tandem mass spectrometry determination of bumetanide in human plasma and application to a clinical pharmacokinetic study, Biomed Chromatogr. (2024) e5825.
[135] S.F. Teunissen, N.G. Jager, H. Rosing, A.H. Schinkel, J.H. Schellens, J.H. Beijnen, Development and validation of a quantitative assay for the determination of tamoxifen and its five main phase I metabolites in human serum using liquid chromatography coupled with tandem mass spectrometry, J Chromatogr B Analyt Technol Biomed Life Sci. 879 (19) (2011) 1677–1685.
[136] D.A. Vargas Medina, E.V.S. Maciel, F.M. Lanças, Chapter 26 - Mass spectrometric detection, instrumentation, and ionization methods, in: S. Fanali, B. Chankvetadze, P.R. Haddad, C.F. Poole, M.-.-L. Riekkola (Eds.), Liquid Chromatography, (Third Edition)., Elsevier, 1, 2023, pp. 679–706.
[137] R. Pisano, M. Breda, S. Grassi, C.A. James, Hydrophilic interaction liquid chromatography-APCI-mass spectrometry determination of 5-fluorouracil in plasma and tissues, J Pharm Biomed Anal. 38 (4) (2005) 738–745.
[138] D. Montange, M. Berard, M. Demarchi, P. Muret, S. Piedoux, J.P. Kantelip, et al, An APCI LC-MS/MS method for routine determination of capecitabine and its metabolites in human plasma, J Mass Spectrom. 45 (6) (2010) 670–677.
[139] S. Achanta, M. Ngo, A. Veitenheimer, L.K. Maxwell, J.R. Wagner, Simultaneous quantification of vinblastine and desacetylvinblastine concentrations in canine plasma and urine samples using LC-APCI-MS/MS, J Chromatogr B Analyt Technol Biomed Life Sci. 913–914 (2013) 147–154.
[140] S. Nabhani Gebara, S. Barton, I. Appleford, P. McCalla, G. Sewell, R. Sabbagh Dit Hawasli, Consensus recommendations for the safe handling of cytotoxic agents in cytotoxic academic research laboratories (CARL), J Oncol Pharm Pract. 26 (8) (2020) 1953–1963.
[141] N. Guichard, J. Boccard, S. Rudaz, P. Bonnabry, S.F. Souverain, Wipe-sampling procedure optimisation for the determination of 23 antineoplastic drugs used in the hospital pharmacy, Eur J Hosp Pharm. 28 (2) (2021) 94–99.
[142] S. von Grunigen, L. Falaschi, N. Guichard, S. Fleury-Souverain, A. Geissbuhler, P. Bonnabry, Development and proof of concept of an audit toolkit for the safe handling of cytotoxic drugs in low- and middle-income countries, JCO Glob Oncol. 7 (2021) 1480–1489.
[143] B. Basu, B.G. Prajapati, S. Mukherjee, T.K. Roy, A. Roy, C.M. Hossain, et al, Therapeutic drug monitoring (TDM) and toxicological studies in alternative biological matrices, in: S.K. Amponsah, Y.V. Pathak (Eds.), Recent Advances in Therapeutic Drug Monitoring and Clinical Toxicology, Springer International Publishing, Cham, 2022, pp. 95–116.
[144] J. Descoeur, A.M. Dupuy, A.S. Bargnoux, J.P. Cristol, O. Mathieu, Comparison of four immunoassays to an HPLC method for the therapeutic drug monitoring of methotrexate: Influence of the hydroxylated metabolite levels and impact on clinical threshold, J Oncol Pharm Pract. 28 (1) (2022) 55–63.
[145] S. Tajik, M.A. Taher, H. Beitollahi, M. Torkzadeh-Mahani, Electrochemical determination of the anticancer drug taxol at a ds-DNA modified pencil-graphite electrode and its application as a label-free electrochemical biosensor, Talanta. 134 (2015) 60–64.
[146] C. Baj-Rossi, G. De Micheli, S. Carrara, Electrochemical detection of anti-breast-cancer agents in human serum by cytochrome P450-coated carbon nanotubes, Sensors (basel). 12 (5) (2012) 6520–6537.
[147] F. Rodino, M. Bartoli, S. Carrara, Simultaneous and selective detection of etoposide and methotrexate with single electrochemical sensors for therapeutic drug monitoring, IEEE Sensor Lett. 7 (8) (2023).
[148] P. Courlet, S. Alves Saldanha, M. Cavassini, C. Marzolini, E. Choong, C. Csajka, et al, Development and validation of a multiplex UHPLC-MS/MS assay with stable isotopic internal standards for the monitoring of the plasma concentrations of the antiretroviral drugs bictegravir, cabotegravir, doravirine, and rilpivirine in people living with HIV, J Mass Spectrom. 55 (6) (2020) e4506.
[149] L.A. Decosterd, T. Mercier, B. Ternon, S. Cruchon, N. Guignard, S. Lahrichi, et al, Validation and clinical application of a multiplex high performance liquid chromatography - tandem mass spectrometry assay for the monitoring of plasma concentrations of 12 antibiotics in patients with severe bacterial infections, J Chromatogr B Analyt Technol Biomed Life Sci. 1157 (2020) 122160.
[150] C.E. Knezevic, W. Clarke, Cancer chemotherapy: The case for therapeutic drug monitoring, Ther Drug Monit. 42 (1) (2020) 6–19.
[151] D. Leveque, G. Becker, The role of therapeutic drug monitoring in the management of safety of anticancer agents: a focus on 3 cytotoxics, Expert Opin Drug Saf. 18 (11) (2019) 1009–1015.
[152] I.H. Bartelink, A. Lalmohamed, E.M. van Reij, C.C. Dvorak, R.M. Savic, J. Zwaveling, et al, Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis, Lancet Haematol. 3 (11) (2016) e526–e536.
[153] K. Ben Hassine, T. Nava, Y. Theoret, C.E. Nath, Y. Daali, N. Kassir, et al, Precision dosing of intravenous busulfan in pediatric hematopoietic stem cell transplantation: Results from a multicenter population pharmacokinetic study, CPT Pharmacometrics Syst Pharmacol. 10 (9) (2021) 1043–1056.
[154] C. Seydoux, R. Battegay, J. Halter, D. Heim, K.M. Rentsch, J.R. Passweg, et al, Impact of busulfan pharmacokinetics on outcome in adult patients receiving an allogeneic hematopoietic cell transplantation, Bone Marrow Transplant. 57 (6) (2022) 903–910.
[155] S. Barnett, G. Makin, D.A. Tweddle, C. Osborne, G.J. Veal, Generation of evidence-based carboplatin dosing guidelines for neonates and infants, Br J Cancer. 129 (11) (2023) 1773–1779.
[156] J.K. Duong, G.J. Veal, C.E. Nath, P.J. Shaw, J. Errington, R. Ladenstein, et al, Population pharmacokinetics of carboplatin, etoposide and melphalan in children: a re-evaluation of paediatric dosing formulas for carboplatin in patients with normal or mild impairment of renal function, Br J Clin Pharmacol. 85 (1) (2019) 136–146.
[157] C.E. Nath, J. Trotman, C. Tiley, P. Presgrave, D. Joshua, I. Kerridge, et al, High melphalan exposure is associated with improved overall survival in myeloma patients receiving high dose melphalan and autologous transplantation, Br J Clin Pharmacol. 82 (1) (2016) 149–159.
[158] D.H. Salinger, J.S. McCune, A.G. Ren, D.D. Shen, J.T. Slattery, B. Phillips, et al, Real-time dose adjustment of cyclophosphamide in a preparative regimen for hematopoietic cell transplant: a Bayesian pharmacokinetic approach, Clin Cancer Res. 12 (16) (2006) 4888–4898.
[159] A.D. Huitema, R.A. Mathot, M.M. Tibben, S. Rodenhuis, J.H. Beijnen, Validation of a therapeutic drug monitoring strategy for thiotepa in a high-dose chemotherapy regimen, Ther Drug Monit. 23 (6) (2001) 650–657.
[160] C. Fernandez-Teruel, S. Fudio, R. Lubomirov, Integrated exposure-response analysis of efficacy and safety of lurbinectedin to support the dose regimen in small-cell lung cancer, Cancer Chemother Pharmacol. 89 (5) (2022) 585–594.
[161] R.J. Motzer, M. Mazumdar, J. Sheinfeld, D.F. Bajorin, H.A. Macapinlac, M. Bains, et al, Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumor patients, J Clin Oncol. 18 (6) (2000) 1173–1180.
[162] F. Lemaitre, F. Goirand, M. Launay, E. Chatelut, J.C. Boyer, A. Evrard, et al, 5-fluorouracil therapeutic drug monitoring: Update and recommendations of the STP-PT group of the SFPT and the GPCO-Unicancer, Bull Cancer. 105 (9) (2018) 790–803.
[163] A. Nagamine, T. Araki, H. Yashima, A. Kamimura, T. Shiraishi, T. Yanagawa, et al, Target concentration achievement for efficacy and safety of patients with osteosarcoma treated with high-dose methotrexate based on individual pharmacokinetics: A retrospective study, Oncol Lett. 25 (2) (2023) 70.
[164] B.C. Widemann, P.C. Adamson, Understanding and managing methotrexate nephrotoxicity, Oncologist. 11 (6) (2006) 694–703.
[165] R.B. Gearry, M.L. Barclay, Azathioprine and 6-mercaptopurine pharmacogenetics and metabolite monitoring in inflammatory bowel disease, J Gastroenterol Hepatol. 20 (8) (2005) 1149–1157.
[166] T.A. de Beaumais, S. Lorrain, N. Mamhoudi, M. Simonin, C. Martinez Vinson, Y. Medard, et al, Key factors associated with 6-thioguanine and 6-methylmercaptopurine nucleotide concentrations in children treated by thiopurine for acute leukaemia and inflammatory bowel disease, Br J Clin Pharmacol. 90 (1) (2024) 209–219.
[167] N. de Rouw, S. Croes, R. Posthuma, D.E. Agterhuis, J. Schoenmaekers, H.J. Derijks, et al, Pharmacokinetically-guided dosing of pemetrexed in a patient with renal impairment and a patient requiring hemodialysis, Lung Cancer. 130 (2019) 156–158.

[168] F.K. Engels, W.J. Loos, J.M. van der Bol, P. de Bruijn, R.H. Mathijssen, J. Verweij, et al, Therapeutic drug monitoring for the individualization of docetaxel dosing: a randomized pharmacokinetic study, Clin Cancer Res. 17 (2) (2011) 353–362.
[169] M.H. Woo, M.V. Relling, D.S. Sonnichsen, G.K. Rivera, C.B. Pratt, C.H. Pui, et al, Phase I targeted systemic exposure study of paclitaxel in children with refractory acute leukemias, Clin Cancer Res. 5 (3) (1999) 543–549.
[170] M. Joerger, J. von Pawel, S. Kraff, J.R. Fischer, W. Eberhardt, T.C. Gauler, et al, Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC), Ann Oncol. 27 (10) (2016) 1895–1902.
[171] B.C. Agema, S.A.J. Buck, M. Viskil, K.T. Isebia, M.J. de Neijs, S.D.T. Sassen, et al, Early identification of patients at risk of cabazitaxel-induced severe neutropenia, Eur Urol Oncol. (2023).
[172] S. Barnett, F. Hellmann, E. Parke, G. Makin, D.A. Tweddle, C. Osborne, et al, Vincristine dosing, drug exposure and therapeutic drug monitoring in neonate and infant cancer patients, Eur J Cancer. 164 (2022) 127–136.
[173] O. Majid, A. Gupta, L. Reyderman, M. Olivo, Z. Hussein, Population pharmacometric analyses of eribulin in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes, J Clin Pharmacol. 54 (10) (2014) 1134–1143.
[174] G. Freyer, B. Ligneau, B. Tranchand, C. Ardiet, P.J. Souquet, I. Court-Fortune, et al, The prognostic value of etoposide area under the curve (AUC) at first chemotherapy cycle in small cell lung cancer patients: a multicenter study of the groupe Lyon-Saint-Etienne d'Oncologie Thoracique (GLOT), Lung Cancer. 31 (2–3) (2001) 247–256.
[175] S.P. Lowis, L. Price, A.D. Pearson, D.R. Newell, M. Cole, A study of the feasibility and accuracy of pharmacokinetically guided etoposide dosing in children, Br J Cancer. 77 (12) (1998) 2318–2323.
[176] C.M. van Tilburg, T. Milde, R. Witt, J. Ecker, T. Hielscher, A. Seitz, et al, Phase I/II intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma, or leukemia, Clin Epigenetics. 11 (1) (2019) 188.
[177] G. Corona, E. Di Gregorio, A. Buonadonna, D. Lombardi, S. Scalone, A. Steffan, et al, Pharmacometabolomics of trabectedin in metastatic soft tissue sarcoma patients, Front Pharmacol. 14 (2023) 1212634.
[178] G.A. Smith, L.E. Damon, H.S. Rugo, C.A. Ries, C.A. Linker, High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency, J Clin Oncol. 15 (2) (1997) 833–839.
[179] S. Han, Y.J. Kim, J. Lee, S. Jeon, T. Hong, G.J. Park, et al, Model-based adaptive phase I trial design of post-transplant decitabine maintenance in myelodysplastic syndrome, J Hematol Oncol. 8 (2015) 118.
[180] C. Serdjebi, F. Gattacceca, J.F. Seitz, F. Fein, J. Gagniere, E. Francois, et al, Population pharmacokinetics of gemcitabine and dFdU in pancreatic cancer patients using an optimal design, Sparse Sampling Approach. Ther Drug Monit. 39 (3) (2017) 290–296.
[181] C.R. Petri, P.H. O'Donnell, H. Cao, A.S. Artz, W. Stock, A. Wickrema, et al, Clofarabine-associated acute kidney injury in patients undergoing hematopoietic stem cell transplant, Leuk Lymphoma. 55 (12) (2014) 2866–2873.
[182] D.R. Barpe, D.D. Rosa, P.E. Froehlich, Pharmacokinetic evaluation of doxorubicin plasma levels in normal and overweight patients with breast cancer and simulation of dose adjustment by different indexes of body mass, Eur J Pharm Sci. 41 (3–4) (2010) 458–463.
[183] P. Thompson, H.E. Wheeler, S.M. Delaney, R. Lorier, U. Broeckel, M. Devidas, et al, Pharmacokinetics and pharmacogenomics of daunorubicin in children: a report from the Children's Oncology Group, Cancer Chemother Pharmacol. 74 (4) (2014) 831–838.
[184] S. Varatharajan, J.C. Panetta, A. Abraham, S. Karathedath, E. Mohanan, K.M. Lakshmi, et al, Population pharmacokinetics of Daunorubicin in adult patients with acute myeloid leukemia, Cancer Chemother Pharmacol. 78 (5) (2016) 1051–1058.
[185] R. Ansaar, R. Meech, A. Rowland, A physiologically based pharmacokinetic model to predict determinants of variability in epirubicin exposure and tissue distribution, Pharmaceutics. 15 (4) (2023).
[186] D. Marchiset-Leca, F.R. Leca, A. Galeani, A. Noble, A. Iliadis, A limited sampling strategy for the study of pirarubicin pharmacokinetics in humans, Cancer Chemother Pharmacol. 36 (3) (1995) 233–238.
[187] M. White-Koning, C. Osborne, A. Paci, A.V. Boddy, E. Chatelut, G.J. Veal, Investigating the potential impact of dose banding for systemic anti-cancer therapy in the paediatric setting based on pharmacokinetic evidence, Eur J Cancer. 91 (2018) 56–67.
[188] V. Carruthers, S. Barnett, R. Rees, T. Arif, O. Slater, R. Ramanujachar, et al, Clinical utility of vinblastine therapeutic drug monitoring for the treatment of infantile myofibroma patients: A case series, Pediatr Blood Cancer. 69 (7) (2022) e29722.
[189] R. Fanciullino, C. Mercier, C. Serdjebi, Y. Berda, F. Fina, L. Ouafik, et al, Lethal toxicity after administration of azacytidine: implication of the cytidine deaminase-deficiency syndrome, Pharmacogenet Genomics. 25 (6) (2015) 317–321.
[190] R. Fanciullino, C. Mercier, C. Serdjebi, G. Venton, J. Colle, F. Fina, et al, Yin and yang of cytidine deaminase roles in clinical response to azacitidine in the elderly: a pharmacogenetics tale, Pharmacogenomics. 16 (17) (2015) 1907–1912.
[191] A. Gaudy, E. Laille, R. Bailey, S. Zhou, B. Skikne, C.L. Beach, Population pharmacokinetics of oral azacitidine, and exposure-response analysis in acute myeloid leukemia, Clin Pharmacol Ther. 114 (4) (2023) 845–852.
[192] N. Takebe, J.H. Beumer, S. Kummar, B.F. Kiesel, A. Dowlati, G. O'Sullivan Coyne, et al, A phase I pharmacokinetic study of belinostat in patients with advanced cancers and varying degrees of liver dysfunction, Br J Clin Pharmacol. 85 (11) (2019) 2499–2511.
[193] L. Yang, X.C. Zhang, S.F. Yu, H.Q. Zhu, A.P. Hu, J. Chen, et al, Pharmacokinetics and safety of cyclophosphamide and docetaxel in a hemodialysis patient with early stage breast cancer: a case report, BMC Cancer. 15 (2015) 917.
[194] L. Alnaim, Therapeutic drug monitoring of cancer chemotherapy, J Oncol Pharm Pract. 13 (4) (2007) 207–221.
[195] F. Kluwe, R. Michelet, A. Mueller-Schoell, C. Maier, L. Klopp-Schulze, M. van Dyk, et al, Perspectives on model-informed precision dosing in the digital health era: Challenges, opportunities, and recommendations, Clin Pharmacol Ther. 109 (1) (2021) 29–36.
[196] G.J. Veal, E.B. Amankwatia, M.N. Paludetto, T. Mocklinghoff, F. Thomson, N. Andre, et al, Pharmacodynamic therapeutic drug monitoring for cancer: Challenges, Advances, and future opportunities, Ther Drug Monit. 41 (2) (2019) 142–159.
[197] Y. Shiravand, F. Khodadadi, S.M.A. Kashani, S.R. Hosseini-Fard, S. Hosseini, H. Sadeghirad, et al, Immune checkpoint inhibitors in cancer therapy, Curr Oncol. 29 (5) (2022) 3044–3060.
[198] C. Seydoux, M. Medinger, S. Gerull, J. Halter, D. Heim, Y. Chalandon, et al, Busulfan-cyclophosphamide versus cyclophosphamide-busulfan as conditioning regimen before allogeneic hematopoietic cell transplantation: a prospective randomized trial, Ann Hematol. 100 (1) (2021) 209–216.
[199] Z. Fang, H. Zhang, J. Guo, J. Guo, Overview of therapeutic drug monitoring and clinical practice, Talanta. 266 (Pt 1) (2023) 124996.
[200] S. Barnett, V. Holden, Q. Campbell-Hewson, G.J. Veal, Perspectives and expertise in establishing a therapeutic drug monitoring programme for challenging childhood cancer patient populations, Front Oncol. 11 (2021) 815040.
[201] https://www.trc-canada.com/.
[202] https://www.alsachim.com/en/.
[203] E. Choong, C.R.S. Uppugunduri, D. Marino, M. Kuntzinger, F. Doffey-Lazeyras, R. Lo Piccolo, et al, therapeutic drug monitoring of busulfan for the management of pediatric patients: Cross-validation of Methods and Long-Term Performance, Ther Drug Monit. 40 (1) (2018) 84–92.
[204] Assurance Qualité des Laboratoires de Biologie Médicale [Available from: https://www.asqualab.com/programmes_recherche_examen.html.
[205] https://www.skml.nl/en/home/sections/drug-analysis-and-toxicology-kkgt.
[206] H. Bourgeois, J. Vermorken, G. Dark, et al, Evaluation of oral versus intravenous dose of vinorelbine to achieve equivalent blood exposures in patients with solid tumours, Cancer Chemother. Pharmacol. 60 (2007) 407–413, https://doi.org/10.1007/s00280-007-0510-z.