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Importance of Sex-Dependent Differences for Dosing Selection and Optimization of Chemotherapeutic Drugs

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Abstract

Background: Despite major advances in cancer treatment in the past years, there is a need to optimize chemotherapeutic drug dosing strategies to reduce toxicities, suboptimal responses, and the risk of relapse. Most cancer drugs have a narrow therapeutic index with substantial pharmacokinetics variability. Yet, current dosing approaches do not fully account for the complex pathophysiological characteristics of the patients. In this regard, the effect of sex on anticancer chemotherapeutic drugs' disposition is still underexplored. In this article, we review sex differences in chemotherapeutic drug pharmacokinetics; we suggest a novel approach that integrates sex into the traditional a priori body surface area (BSA) dosing selection model, and finally, we provide an overview of the potential benefits of a broader use of therapeutic drug monitoring (TDM) in oncology. ***Summary:*** To date, anticancer chemotherapeutic drug dosing is most often determined by BSA, a method widely used for its ease of practice, despite criticism for not accounting for individual factors, notably sex. Anatomical, physiological, and biological differences between males and females can affect pharmacokinetics, including drug metabolism and clearance. At equivalent doses, females tend to display higher circulating exposure and more organ toxicities, which has been formally demonstrated at present for about 20% of chemotherapeutic drugs. An alternative could be the sex-adjusted BSA (SABSA), incorporating a 10% increase in dosing for males and a 10% decrease for females, though this approach still lacks formal clinical validation. Another strategy to reduce treatment-related toxicity and potentially enhance clinical outcomes could be a more widespread use

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of TDM, for which a benefit has been demonstrated for 5-fluorouracil, busulfan, methotrexate, or thiopurines. ***Key Messages:*** The inclusion of sex besides BSA in an easy-to-implement formula such as SABSA could improve a priori chemotherapy dosing selection, even though it still requires clinical validation. The a posteriori use of TDM could further enhance treatment efficacy and safety in oncology.

Introduction

Significant progress has been made over the past 2 decades in the early detection, diagnosis, treatment, and clinical follow-up of cancer patients [1]. Revolutionary discoveries, such as protein kinase inhibitors exemplified by imatinib for the treatment of chronic myeloid leukemia, immunotherapies for many metastatic solid cancers, or chimeric antigen receptor T therapy for hematological neoplasms, are key milestones in the continuous fight against cancer. The progressive improvement in most cancer mortality and morbidity rates is partly due to the development of targeted therapies, monoclonal antibodies, and immunotherapies [1, 2]. The personalization of treatments based on tumor genetic profiling represents another recent milestone [3]. However, despite ongoing drug discoveries, conventional chemotherapies remain one of the principal first-line treatments for almost all hematological or solid cancers. Their use has been strengthened by gradual improvements in the delineation of indications, choice of molecules, or strategies to combine them over the past 50 years [4]. Yet, surprisingly, for the most commonly used chemotherapeutic drugs, there has been much less emphasis on the refinement of the most elementary standard of practice, namely drug *dosage optimization* in the individual patient.

Most cytotoxic drugs display a narrow therapeutic index, significantly affecting their tolerability in case of excessive systemic exposure, or their efficacy in case of insufficient concentration [5, 6]. Maintaining such a balance between acceptable treatment-related toxicity (TRT) and risk of relapse is a constant challenge for oncologists. Given the notable inter-individual pharmacokinetic (PK) variability of most chemotherapeutic drugs, optimizing dosing remains an important challenge to date [6]. Several considerations are used for drug treatment individualization, including demographic characteristics (age, body surface area [BSA], weight), comorbidities (renal and/or hepatic disorders), co-medications (drug-drug interactions), and/or genetic factors (pharmacogenetic polymorphisms). Multiple other strategies have been explored to optimize dosing, such as the switch from oral to intravenous formulations for busulfan [7], treatment rescue with leucovorin for methotrexate (MTX) [8], or therapeutic drug monitoring (TDM) for several anticancer drug classes [6]. However, while genomics is increasingly evoked in personalized therapy, there has been so far only little attention given to the sex-related differences that can impact drug disposition. In this article, we provide an overview of existing data on the effect of sex on chemotherapeutic drugs PK. Furthermore, we present an approach for dosing optimization that considers sex into the traditional a priori BSA-based chemotherapeutic drug dosing selection, and we discuss the additional benefit of the a posteriori dosing adjustment based on TDM in female and male patients.

BSA Drug Dosing and Sex

To date, chemotherapy doses are commonly determined according to either body weight (BW) or BSA. These dosing strategies have not changed much since their implementation in the early 1960s and were initially mostly based on a maximum-tolerated-dose strategy, regardless of significant adverse reactions. The BSA is calculated using the Mosteller formula (BSA in m^2 = [height, cm × weight, kg/3,600]$^{1/2}$) and is primarily adopted because of its ease of application in daily clinical practice. This easy-to-implement formula remains the default approach nowadays, despite being questioned for decades in seminal perspectives and editorial articles: "Body surface area as a basis for dosing of anticancer agents: science, myth, or habit?" [9], "Dosing strategies for anticancer drugs: the good, the bad, and BSA [10]; "Conventional dosing of anticancer agents: precisely wrong or just inaccurate?" [11]. In fact, the large inter-individual variability of most chemotherapeutic drugs was recognized early on, and the reliance on BSA aimed at adjusting dosages to body dimensions, under the elementary assumption that drug clearance by elimination organs is correlated with the lean and metabolically active mass of the body in the absence of pathology. The BSA approach in oncology has been often criticized by clinical pharmacologists due to its poor correlation with the clearance of many drugs, and because it does not consider the complex pathophysiological and clinical conditions of cancer patients [9–11], neither for the most basic patients' characteristics, such as sex [12].

Indeed, as well as depending on body dimensions which differ between women and men, drug disposition has further important sex-related characteristics, influenced notably by sex differences [13, 14] in total body water and lean mass percentages [15], expression of drug-metabolizing enzymes and transport proteins, hormonal regulation, or renal and hepatic clearance due to larger organs in males [16, 17]. One major limitation of BSA-based chemotherapy dosing is that it ignores sex differences in lean mass [15]. For a given BW, a female body contains on average more adipose tissue (350 g/kg compared to 250 g/kg in males) and therefore less lean mass [18, 19]. This difference is substantial, despite some degree of overlap between males and females due to within-gender variability. On the one hand, it affects the distribution of drugs, which tends to occur in a larger volume for lipophilic molecules and in a smaller volume for hydrophilic molecules in females compared to males [20]. On the other hand, it impacts the liver and the kidneys, both organs largely involved in drug elimination, whose level of function is strongly correlated with lean and metabolically active body mass in the absence of pathology. BSA is certainly a better proxy of lean body mass than total BW [19]. Indeed, prescribing in mg/kg of BW is unanimously considered suboptimal as it overestimates the elimination capacity of obese individuals, whose excess weight is mainly adipose tissue. However, prescription in mg/kg of lean body mass would be preferable as fat-free body mass is a better estimate of the size of metabolically active tissues [12, 21, 22]. Altogether, correcting dosages not only for height, weight, and BSA, but also for body composition would significantly reduce the impact of sex differences on drug PK [17].

Sex Impact on Chemotherapeutic Drugs PK

In this context, administering the same dose of chemotherapy to males and females with the same BSA exposes the former to a risk of underdosing and the latter to a risk of overdosing. This common practice of the same doses for males and females can be attributed to the historical exclusion of female patients in clinical studies [16, 23, 24]. This fact originates from the 1977 recommendations of the US Food and Drug Administration (FDA), which suggested that females of childbearing age should not be included in randomized trials due to potential risks [25]. Although later national efforts have been made with updated recommendations, the percentage of female inclusion in trials remained until 2011 below 40% and has not markedly increased in the past years, with most drug doses extrapolated from male metabolism [26]. In cancer patients, a recent meta-analysis showed a similar female enrollment percentage of 35% in clinical trials supporting FDA approvals for solid cancers [27].

In oncology, the influence of sex on the prevalence of cancer, prognosis, and treatment response is well-established and differences in treatment tolerability have been observed in various cancers since the early 2000s [23]. A number of observational studies and post hoc analyses of randomized controlled trials confirm that females are more prone to develop toxic effects of chemotherapies, while males show a higher occurrence of therapeutic failure; both effects could be explained by notably sex-related differences in PK. Although toxic death rates are similar, females tend to experience more hematological and non-hematological toxicities than males in many if not all cancers [16, 28, 29], leading to more delayed treatment and dose reduction [28]. Delayed effects, such as cardiotoxicity occurring years after anthracycline therapy, have also been reported to differ between sexes [30]. The scope of these differences is however difficult to assess as only 0.5% of clinical trials in oncology report adverse drug reactions by sex [31]. As a dose-response relationship has been demonstrated in some cancers [32], it is reasonable to question whether females benefit from their higher systemic exposure in terms of overall response. Though some authors show a higher overall response rate in females compared to males [28, 29, 33], this is not consistently widely supported in the literature [34]. There might be a small benefit in overall survival with specific treatments or certain cancers only, such as acute myeloid leukemia, non-Hodgkin lymphomas, or non-small cell lung cancers [31].

Male/female differences in PK with drug dosage adjustment have already been reported in therapeutic areas other than oncology, such as in the treatment of heart failure [35]. Other commonly used treatments, such as antipsychotics, antibiotics, antiepileptics, and many cardiac drugs (e.g., propranolol, verapamil, digoxin, metoprolol, and even aspirin), display sex differences in PK, though the application in clinical daily practice is very limited and the impact on clinical outcome not always demonstrated [17]. In oncology, in an effort to understand the disparity in clinical outcomes with respect to sex [21, 28, 36], many authors have highlighted the difference in PK between male and female patients [31, 37].

A recent review by the European Society for Medical Oncology analyzed all studies investigating the PK of anticancer chemotherapies [21]. It identified only 80 studies that tested sex as a covariate in drug disposition.

Among these, 41 showed a significant impact of sex on drug PK (either directly or via an estimator of renal function incorporating sex effects). The remaining studies likely did not detect an impact of sex, probably due to lack of statistical power rather than lack of effect. Some drugs may be more prone to sex-related differences in PK and TDM could be particularly useful for some specific treatments. For example, when treated with 5-fluorouracil (5-FU), females display between 15% and 48% lower clearance than males, translating into higher incidences of TRT [37], but without affecting relapse or progression rates [38]. Sex also impacts paclitaxel PK, with females displaying a 16% lower maximal elimination capacity, and dose adaptation permitting a reduction in grade 4 neutropenia though long-term outcomes were not studied [38]. Other drugs' PK, such as doxorubicin [1, 2], irinotecan [3], and temozolomide [4] are also influenced by sex, but the clinical implications in terms of TRT have not been demonstrated. Overall, for the same dosage (calculated in mg/m^2 BSA) of many chemotherapeutics, females are exposed to 15%–25% higher circulating concentrations in blood/plasma compared to males [21].

Sex-Adjusted BSA, the a priori BSA-Based Dosing Selection Adjusted for Sex

Oncologists have tried to overcome the limitations of BSA for dosing selection by including some of this PK variability into easy-to-implement BSA formulas. This includes, among other methods, BSA-adjusted doses based on the ideal BW for obese patients [39] or dosing based on toxicity or response [40, 41]. Overall, considerations for sex-adjusted dosing in oncology, though increasingly recognized, have not been implemented in clinical practice. One alternative for the easy implementation of sex in treatment dosing might be the so-called sex-adjusted body surface area (SABSA). It is proposed that adjusting doses of anticancer chemotherapies based on BSA could be further modulated according to sex, increasing the dose by 10% for males and decreasing it by 10% for females. This ±10% dose modification would be simple to implement in clinical practice at essentially no cost as chemotherapies are nowadays often prepared in central hospital pharmacies or oncology clinics by professionals familiar with BSA calculations using the Mosteller formula. The proposed SABSA is equal to SABSA = BSA × 1.1 for males and SABSA = BSA × 0.9 for females. It is presumed that the widespread adoption of SABSA instead of BSA in dose calculations for suitable chemotherapeutic agents would lead to an overall improvement of both the efficacy and tolerability of these drugs [15]. Of course, this SABSA approach would first need to be formally evaluated in clinical studies, starting with chemotherapeutic drugs for which male/female differences in PK are well recognized, such as 5-FU [37].

TDM to Overcome PK Variability on Oncology

Apart from sex [16, 17, 21], drug PK is obviously influenced by other intrinsic characteristics (body mass index, renal and hepatic function, pathophysiological conditions, expression of drug-metabolizing enzymes or drug transporters, hormonal regulation, and pharmacogenetics) and exogenous factors (e.g., drug-drug interactions, environmental influences, food, lifestyle habits (sport, smoke, etc.) that also contribute independently to the overall variability in drug disposition [16, 17]. While the SABSA formula applied for the determination of the first dose of chemotherapeutics would represent an initial attempt to account for sex in chemotherapy dosing, such calculation cannot be expected to reflect the complex influences of all other aforementioned factors combined. In contrast, drug concentration measured in plasma (i.e., TDM) constitutes the final phenotypic trait and best available marker of the patient's drug exposure, integrating not only sex-related differences but also all genetic and non-genetic influences, and allowing for refined a posteriori drug dosage adjustment.

TDM as a standard of care is current practice in many places for various antibiotics, antiepileptics, immunosuppressants, antifungals, antidepressants, antipsychotics, and HIV drugs [42, 43]. In oncology, several clinical PK studies have confirmed the considerable inter-individual variability that characterizes commonly used anticancer chemotherapies and, yet more rarely, the potential impact of PK on outcomes (reviewed notably by Paci et al. [6]). However, despite being repeatedly advocated – mostly by clinical pharmacologists – for many anticancer drugs [6, 44–48], TDM is generally not performed in routine oncological care, with the exceptions of MTX, busulfan, thiopurine drugs, and 5-FU as their concentrations measured in blood have been demonstrated to predict their clinical efficacy and/or toxicity better than the administered dose. Moreover, these drugs are characterized by notable inter-individual PK variability, narrow therapeutic index, high risk of drug-drug interactions, and sex-dependent differences.

MTX, Busulfan, Thiopurines, and 5-FU: TDM and Sex Differences

MTX is the most commonly implemented agent subjected to TDM, which is typically performed to adapt leucovorin rescue dosage and duration rather than to modify MTX dose, although a mean MTX concentration comprised within 1,000–1,500 μmol/L should be reached to ensure optimal anti-tumoral efficacy [8, 49]. Population PK analyses of BSA-adjusted dosing of high-dose MTX revealed an effect of sex [50] on MTX clearance with a 16% lower clearance in females compared to males [51]. A recent systematic review of population PK models for MTX confirmed the impact of sex on MTX PK [52].

In allogeneic hematopoietic stem cell transplantation settings, busulfan TDM [53] is usually performed on the first day of the 4-day conditioning regimen to achieve an ideal target range of 3,600–6,000 μmol/L*min to limit its toxicity while permitting efficient myeloablation [54]. Inter-sex differences in busulfan distribution volume have been reported [55]. Population PK analyses confirmed the effect of sex on busulfan PK [56]. Noteworthy, while TDM is widely considered essential to ensure sufficient and safe busulfan exposure in pediatric and adult populations [57, 58], only a minority (<20%) of transplant centers perform it [59].

TDM of thiopurine drugs (6-mercaptopurine, thioguanine, and azathioprine), namely the blood measurement of their intracellular metabolites thioguanine nucleotides (6-TGN) and 6-methyl-mercaptopurine (6-MMP), may also be performed [60, 61] since polymorphisms in the thiopurine methyl-transferase (TPMT) gene affect their metabolism, as well as myelosuppression and hepatotoxicity potential [62, 63]. Therapeutic ranges of 6-TGN in blood (established in patients with inflammatory bowel disease) are within 250–450 pmol/8 × 10^8 erythrocytes in adults (235–450 pmol/8 × 10^8 erythrocytes in children) [61, 64–66]. 6-MMP is devoid of therapeutic effect, but 6-MMP concentrations exceeding 5,700 pmol/8 × 10^8 erythrocytes are associated with an increased risk of hepatotoxicity [64, 67]. Sex differences have been reported for thiopurine drugs [68, 69]. In children with acute lymphoblastic leukemia, there is a boy/girl difference in 6-mercaptopurine utilization [70] and tolerance [71]. In human liver biopsies, TPMT activity is 14% higher in men than in females [72]. Likewise, higher TPMT activity has been also reported in male children compared with female children and adults of normal genotype [73]. Sex should therefore be considered in evaluating TPMT activity or thiopurines' adverse effects [74].

Finally, efforts toward dose individualization based on PK to optimize 5-FU chemotherapies have shown a very poor correlation between BSA and 5-FU clearance [75]. In fact, less than 10% of the patients have plasma levels within the therapeutic range – i.e., a target area under the curve of 20–25 mg·h/L [76, 77] – when 5-FU dose is solely based on BSA. This fraction is increased to 94% by TDM, which reduces toxicity [78] and significantly improves the response rate [79]. 5-FU is metabolized by the polymorphic dihydropyrimidine dehydrogenase (DPD) enzyme, whose activity is deficient in up to 8% of the Caucasian population. Genetic testing for DPD deficiency prior to 5-FU-based treatment has been recommended since 2020 by the European Medicines Agency to identify patients for whom the dose needs to be preemptively adapted [80]. Conversely, phenotyping DPD by ex vivo enzymatic assay or using a surrogate test (i.e., the measurement of physiological *uracil* or *dihydrouracil* to *uracil ratio* in plasma) has been proposed to detect DPD deficiency [81]. Lastly, of particular interest, a notable sex-specific difference in elimination has been noted for 5-FU [37, 82].

Extending TDM to Less Well-Studied Chemotherapeutic Agents

Overall, the distinct sex-related effects reported for the chemotherapeutic agents commonly subjected to TDM (MTX, busulfan, thiopurines, 5-FU) are directly reflected in patients' blood levels that can be readily used for drug dosing adjustment. One could thus argue that neglecting sex differences in the initial dosage would be less harmful for those treatments benefiting from TDM. Conversely, TDM for other chemotherapeutic drugs is at present only sporadically performed and is mostly motivated by suspected toxicity or in case of non-response, but rarely as a systematic standard monitoring [6] and certainly without consideration of sex differences.

Nevertheless, an important inter-individual PK variability characterizes a majority of common chemotherapeutic drugs, which are thus potential candidates for TDM. To date, most of them have not shown definite benefits of TDM in terms of outcomes, but data are scarce given the generally limited interest in the PK of chemotherapeutic agents. For instance, etoposide shows a bioavailability ranging from 25% to 75%, with a concentration exposure varying up to 15-fold in a population receiving the same oral dose [83]. However, PK analyses of high-dose etoposide in patients with

advanced germ cell tumors failed to reveal a significant impact of PK on clinical outcomes, despite a trend toward higher exposure in patients responding to treatment [84]. Cyclophosphamide also exhibits substantial clearance variability of up to 60% in children [85]. Its TDM, involving the measurement of hydroxycyclophosphamide and carboxyethyl-phosphoramide mustard, is challenging [48] and its benefit on outcome has yet to be demonstrated [86]. The active metabolite of ifosfamide, 4-hydroxyifosfamide, also shows a clearance variability of up to 46% along with dose-related adverse events [87], but there are limited data on overall clinical outcomes in large populations. Finally, anthracyclines, such as doxorubicin, epirubicin, daunorubicin, and idarubicin, are known to cause dose-dependent myocardial toxicity [88], though the correlation between PK and adverse event reactions remains controversial [89].

Even though TDM is recognized as one of the most advanced achievements of precision medicine, it is poorly implemented in oncology. Yet, it could likely account for all factors, including sex, that largely contribute to the PK variability of anticancer chemotherapies. TDM may also be of help in specific situations, such as guiding dose selection in case of drug-drug interactions (e.g., concomitant chemotherapy during prolonged or chronic treatment with CYP3A4 inducers such as rifampicin, CYP3A4 inhibitors such as amiodarone, or antifungal azoles), or in special populations for whom information on drug disposition is generally limited, such as pediatric or elderly patients. As treatment indications continue to expand each year, anticancer drugs may likely be administered to an increasingly aging population suffering from chronic conditions (hypertension, cardiovascular diseases, diabetes, neurocognitive impairment, and a resulting definite risk of poly-medication), leading to complex drug associations with high potential for drug-drug interactions, which could adequately be addressed by TDM.

Several organizational and medical constraints can explain the poor implementation of TDM for chemotherapeutic agents in routine clinical practice. Among these are analytical barriers: hospital centers must have sufficiently advanced laboratories capable of tandem mass spectrometry analysis of various chemotherapeutic agents [48, 90], and a TDM service with expertise in chemotherapeutic drug level interpretation should be available. TDM Service should be organized for also providing real-time results as some drug PK needs to be determined within a limited time for dose adjustment, such as with the 2-day protocol for busulfan, for instance [6, 91]. Additionally, some drugs lack internationally recognized systemic exposure targets. These TDM calculations can be facilitated using newly developed model-informed precision dosing software, such as Tucuxi (http://www.tucuxi.ch/), developed by the School of Engineering and Management (HEIG-VD//HES-SO) and the Lausanne University Hospital [92, 93]. The Tucuxi software helps practitioners in the therapeutics-oriented interpretation of drug concentration measurements using Bayesian calculations based on comprehensive reference data, served through a user-friendly graphical interface [93]. Tucuxi has notably been applied to implement and cross-validate a population PK model for busulfan in model-informed precision dosing in children hematopoietic stem cell transplant settings, showing good agreements between the estimated area under the curve and the predicted dose [94]. Moreover, is emerging now in literature the idea of developing new point-of-care technologies to monitor drugs with a more patient-centric process toward precision medicine [95]. At the same time, simple and low-cost electrochemical sensors are proposed for measuring many of the commonly used cancer drugs, including while not limited to etoposide [96], MTX [96], 5-FU [97], ifosfamide [98], and cyclophosphamide [98].

Conclusion

Drugs' disposition generally exhibits significant sex-related differences, influenced notably by variations in male and female body composition, which are not addressed when using the traditional BSA-based drug dosing. The proposed approach of SABSA for chemotherapy dosing selection in male and female patients would represent a further refinement toward sex-dependent personalization in the clinical use of chemotherapeutic agents. While this approach may have limited impact at the individual level, it could benefit a significant number of female and male patients, if one considers the prevalence of cancer, with significant implications for public health. To date, the SABSA approach requires formal clinical validation to assess its ability to effectively reduce inter-gender differences in PK, which could, in turn, help decrease instances of severe toxicity and improve clinical outcomes. Nevertheless, accounting for sex differences through the a priori SABSA dosing selection, followed by a posteriori TDM-guided dose adjustment, which integrates not only sex-related but also genetic and non-genetic

influences, could help prevent severe TRTs and potentially improve clinical outcomes. Other genetic and non-genetic factors not addressed by SABSA and/or TDM may further contribute to improved outcomes in the future as the field of precision oncology is probably only at its beginning.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

C.S., A.D.W., M.B., T.B., and L.A.D. performed the literature review and wrote the manuscript. E.C., M.G., S.C., Y.T., F.L., F.R.G., C.M. critically revised the draft for important intellectual content. All authors contributed to the manuscript and reviewed and approved the final version of the manuscript.

References

1 Santucci C, Carioli G, Bertuccio P, Malvezzi M, Pastorino U, Boffetta P, et al. Progress in cancer mortality, incidence, and survival: a global overview. Eur J Cancer Prev. 2020;29(5):367–81. https://doi.org/10.1097/CEJ.0000000000000594

2 Arnold M, Rutherford MJ, Bardot A, Ferlay J, Andersson TM, Myklebust TA, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol. 2019;20(11):1493–505. https://doi.org/10.1016/S1470-2045(19)30456-5

3 Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. Nat Rev Clin Oncol. 2018;15(6):353–65. https://doi.org/10.1038/s41571-018-0002-6

4 https://www.cancer.gov/research/progress/250-years-milestones

5 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. https://doi.org/10.3389/fonc.2022.1015200

6 Paci A, Veal G, Bardin C, Leveque D, Widmer N, Beijnen J, et al. Review of therapeutic drug monitoring of anticancer drugs part 1--cytotoxics. Eur J Cancer. 2014;50(12):2010–9. https://doi.org/10.1016/j.ejca.2014.04.014

7 Andersson BS, Madden T, Tran HT, Hu WW, Blume KG, Chow DS, et al. Acute safety and pharmacokinetics of intravenous busulfan when used with oral busulfan and cyclophosphamide as pretransplantation conditioning therapy: a phase I study. Biol Blood Marrow Transpl. 2000;6(5A):548–54. https://doi.org/10.1016/s1083-8791(00)70064-4

8 Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. Oncologist. 2016;21(12):1471–82. https://doi.org/10.1634/theoncologist.2015-0164

9 Ratain MJ. Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit? J Clin Oncol. 1998;16(7):2297–8. https://doi.org/10.1200/JCO.1998.16.7.2297

10 Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. Eur J Cancer. 2002;38(13):1677–84. https://doi.org/10.1016/s0959-8049(02)00151-x

11 Bins S, Ratain MJ, Mathijssen RH. Conventional dosing of anticancer agents: precisely wrong or just inaccurate? Clin Pharmacol Ther. 2014;95(4):361–4. https://doi.org/10.1038/clpt.2014.12

12 Gurney H. How to calculate the dose of chemotherapy. Br J Cancer. 2002;86(8):1297–302. https://doi.org/10.1038/sj.bjc.6600139

13 Cespedes Feliciano EM, Lee VS, Prado CM, Meyerhardt JA, Alexeeff S, Kroenke CH, et al. Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: the C-SCANS study. Cancer. 2017;123(24):4868–77. https://doi.org/10.1002/cncr.30950

14 Cheng E, Caan BJ, Cawthon PM, Evans WJ, Hellerstein MK, Shankaran M, et al. Body composition, relative dose intensity, and adverse events among patients with colon cancer. Cancer Epidemiol Biomarkers Prev. 2023;32(10):1373–81. https://doi.org/10.1158/1055-9965.EPI-23-0227

15 Wagner AD. Sex differences in cancer chemotherapy effects, and why we need to reconsider BSA-based dosing of chemotherapy. ESMO Open. 2020;5(5):e000770. https://doi.org/10.1136/esmoopen-2020-000770

16 Ozdemir BC, Csajka C, Dotto GP, Wagner AD. Sex differences in efficacy and toxicity of systemic treatments: an undervalued issue in the era of precision oncology. J Clin Oncol. 2018;36(26):2680–3. https://doi.org/10.1200/JCO.2018.78.3290

17 Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143–57. https://doi.org/10.2165/00003088-200948030-00001

18 Imboden MT, Welch WA, Swartz AM, Montoye AH, Finch HW, Harber MP, et al. Reference standards for body fat measures using GE dual energy x-ray absorptiometry in Caucasian adults. PLoS One. 2017;12(4):e0175110. https://doi.org/10.1371/journal.pone.0175110

19 Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051–65. https://doi.org/10.2165/00003088-200544100-00004

20 V. R-Z. Sex and Gender Differences in Pharmacology. Handbook of experimental pharmacology, Springer, Heidelberg; 2012. 602 p.214.

21 Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, et al. Gender medicine and oncology: report and consensus of an ESMO workshop. Ann Oncol. 2019;30(12):1914–24. https://doi.org/10.1093/annonc/mdz414

22 Ozdemir BC, Gerard CL, Espinosa da Silva C. Sex and gender differences in anticancer treatment toxicity: a call for revisiting drug dosing in oncology. Endocrinology. 2022;163(6):bqac058. https://doi.org/10.1210/endocr/bqac058

23 Zhao G, Wang Y, Wang S, Li N. Reporting outcome comparisons by sex in oncology clinical trials. Nat Commun. 2024;15(1):3051. https://doi.org/10.1038/s41467-024-47321-5

24 Geller SE, Koch AR, Roesch P, Filut A, Hallgren E, Carnes M. The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials. Acad Med. 2018;93(4):630–5. https://doi.org/10.1097/ACM.0000000000002027

25 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-gender-differences-clinical-investigations

26 Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? J Womens Health. 2011;20(3):315–20. https://doi.org/10.1089/jwh.2010.2469

27 Wilson BE, Nadler MB, Desnoyers A, Booth CM, Amir E. Meta-analysis of sex and racial subgroup participation rates and differential treatment effects for trials in solid tumor malignancies leading to US Food and Drug Administration registration between 2010 and 2021. Cancer. 2024;130(2):276–86. https://doi.org/10.1002/cncr.35035
28 Singh S, Parulekar W, Murray N, Feld R, Evans WK, Tu D, et al. Influence of sex on toxicity and treatment outcome in small-cell lung cancer. J Clin Oncol. 2005;23(4):850–6. https://doi.org/10.1200/JCO.2005.03.171
29 Klimm B, Reineke T, Haverkamp H, Behringer K, Eich HT, Josting A, et al. Role of hematotoxicity and sex in patients with Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group. J Clin Oncol. 2005;23(31):8003–11. https://doi.org/10.1200/JCO.2005.205.60
30 Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP, et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med. 1995;332(26):1738–43. https://doi.org/10.1056/NEJM199506293322602
31 Kammula AV, Schaffer AA, Rajagopal PS, Kurzrock R, Ruppin E. Outcome differences by sex in oncology clinical trials. Nat Commun. 2024;15(1):2608. https://doi.org/10.1038/s41467-024-46945-x
32 Moreno Garcia V, Olmos D, Gomez-Roca C, Cassier PA, Morales-Barrera R, Del Conte G, et al. Dose-response relationship in phase i clinical trials: a European drug development network (EDDN) collaboration study. Clin Cancer Res. 2014;20(22):5663–71. https://doi.org/10.1158/1078-0432.CCR-14-0719
33 Wheatley-Price P, Le Maitre A, Ding K, Leighl N, Hirsh V, Seymour L, et al. The influence of sex on efficacy, adverse events, quality of life, and delivery of treatment in National Cancer Institute of Canada Clinical Trials Group non-small cell lung cancer chemotherapy trials. J Thorac Oncol. 2010;5(5):640–8. https://doi.org/10.1097/JTO.0b013e3181d40a1b
34 Fresneau B, Hackshaw A, Hawkins DS, Paulussen M, Anderson JR, Judson I, et al. Investigating the heterogeneity of alkylating agents' efficacy and toxicity between sexes: a systematic review and meta-analysis of randomized trials comparing cyclophosphamide and ifosfamide (MAIAGE study). Pediatr Blood Cancer. 2017;64(8). https://doi.org/10.1002/pbc.26457
35 Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. Lancet. 2019;394(10205):1254–63. https://doi.org/10.1016/S0140-6736(19)31792-1
36 Fourie Zirkelbach J, Shah M, Vallejo J, Cheng J, Ayyoub A, Liu J, et al. Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients. J Clin Oncol. 2022;40(30):3489–500. https://doi.org/10.1200/JCO.22.00371
37 Mueller F, Buchel B, Koberle D, Schurch S, Pfister B, Krahenbuhl S, et al. Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study. Cancer Chemother Pharmacol. 2013;71(2):361–70. https://doi.org/10.1007/s00280-012-2018-4
38 Kim J, Ji E, Jung K, Jung IH, Park J, Lee JC, et al. Gender differences in patients with metastatic pancreatic cancer who received FOLFIRINOX. J Pers Med. 2021;11(2):83. https://doi.org/10.3390/jpm11020083
39 Bubalo J, Carpenter PA, Majhail N, Perales MA, Marks DI, Shaughnessy P, et al. Conditioning chemotherapy dose adjustment in obese patients: a review and position statement by the American Society for Blood and Marrow Transplantation practice guideline committee. Biol Blood Marrow Transpl. 2014;20(5):600–16. https://doi.org/10.1016/j.bbmt.2014.01.019
40 Johnson P, Longley J. Should response-adapted therapy now Be the standard of care for advanced hodgkin's lymphoma? Curr Treat Options Oncol. 2017;18(3):15. https://doi.org/10.1007/s11864-017-0460-6
41 Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2002;99(8):2685–93. https://doi.org/10.1182/blood.v99.8.2685
42 Widmer N, Csajka C, Grouzmann E, Decosterd LA, Buclin T, Biollaz J, et al. Suivi thérapeutique des médicaments (I) les principes. Rev Med Suisse. 2008;4(165):1644–8. https://doi.org/10.53738/revmed.2008.4.165.1644
43 Widmer N, Werner D, Grouzmann E, Eap CB, Marchetti O, Fayet A, et al. [Therapeutic drug monitoring: clinical practice]. Rev Med Suisse. 2008;4(165):1649–50.
44 Mueller-Schoell A, Groenland SL, Scherf-Clavel O, van Dyk M, Huisinga W, Michelet R, et al. Therapeutic drug monitoring of oral targeted antineoplastic drugs. Eur J Clin Pharmacol. 2021;77(4):441–64. https://doi.org/10.1007/s00228-020-03014-8
45 Groenland SL, van Eerden RAG, Verheijen RB, Koolen SLW, Moes D, Desar IME, et al. Therapeutic drug monitoring of oral anticancer drugs: the Dutch pharmacology oncology group-therapeutic drug monitoring protocol for a prospective study. Ther Drug Monit. 2019;41(5):561–7. https://doi.org/10.1097/FTD.0000000000000654
46 Centanni M, Moes D, Troconiz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet. 2019;58(7):835–57. https://doi.org/10.1007/s40262-019-00748-2
47 Briki M, Andre P, Thoma Y, Widmer N, Wagner AD, Decosterd LA, et al. Precision oncology by point-of-care therapeutic drug monitoring and dosage adjustment of conventional cytotoxic chemotherapies: a perspective. Pharmaceutics. 2023;15(4):1283. https://doi.org/10.3390/pharmaceutics15041283
48 Briki M, Murisier A, Guidi M, Seydoux C, Buclin T, Marzolini C, et al. Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) methods for the therapeutic drug monitoring of cytotoxic anticancer drugs: an update. J Chromatogr B Analyt Technol Biomed Life Sci. 2024;1236:124039. https://doi.org/10.1016/j.jchromb.2024.124039
49 Leveque D, Santucci R, Gourieux B, Herbrecht R. Pharmacokinetic drug-drug interactions with methotrexate in oncology. Expert Rev Clin Pharmacol. 2011;4(6):743–50. https://doi.org/10.1586/ecp.11.57
50 Zhang C, Zhai S, Yang L, Wu H, Zhang J, Ke X. Population pharmacokinetic study of methotrexate in children with acute lymphoblastic leukemia. Int J Clin Pharmacol Ther. 2010;48(1):11–21. https://doi.org/10.5414/cpp48011
51 Arshad U, Taubert M, Seeger-Nukpezah T, Ullah S, Spindeldreier KC, Jaehde U, et al. Evaluation of body-surface-area adjusted dosing of high-dose methotrexate by population pharmacokinetics in a large cohort of cancer patients. BMC Cancer. 2021;21(1):719. https://doi.org/10.1186/s12885-021-08443-x
52 Zhang Y, Sun L, Chen X, Zhao L, Wang X, Zhao Z, et al. A systematic review of population pharmacokinetic models of methotrexate. Eur J Drug Metab Pharmacokinet. 2022;47(2):143–64. https://doi.org/10.1007/s13318-021-00737-6
53 Marsit H, Philippe M, Neely M, Rushing T, Bertrand Y, Ducher M, et al. Intra-individual pharmacokinetic variability of intravenous busulfan in hematopoietic stem cell-transplanted children. Clin Pharmacokinet. 2020;59(8):1049–61. https://doi.org/10.1007/s40262-020-00877-z
54 Bartelink IH, Lalmohamed A, van Reij EM, Dvorak CC, Savic RM, Zwaveling J, 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. 2016;3(11):e526–36. https://doi.org/10.1016/S2352-3026(16)30114-4
55 McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NH. Busulfan in infant to adult hematopoietic cell transplant recipients: a population pharmacokinetic model for initial and Bayesian dose personalization. Clin Cancer Res. 2014;20(3):754–63. https://doi.org/10.1158/1078-0432.CCR-13-1960

56 Takahashi T, Illamola SM, Jennissen CA, Long SE, Lund TC, Orchard PJ, et al. Busulfan dose recommendation in inherited metabolic disorders: population pharmacokinetic analysis. Transpl Cell Ther. 2022; 28(2):104 e1–e7. https://doi.org/10.1016/j.jtct.2021.11.018
57 Feng X, Wu Y, Zhang J, Li J, Zhu G, Fan D, et al. Busulfan systemic exposure and its relationship with efficacy and safety in hematopoietic stem cell transplantation in children: a meta-analysis. BMC Pediatr. 2020; 20(1):176. https://doi.org/10.1186/s12887-020-02028-6
58 Seydoux C, Battegay R, Halter J, Heim D, Rentsch KM, Passweg JR, et al. Impact of busulfan pharmacokinetics on outcome in adult patients receiving an allogeneic hematopoietic cell transplantation. Bone Marrow Transpl. 2022;57(6):903–10. https://doi.org/10.1038/s41409-022-01641-6
59 Ruutu T, van der Werf S, van Biezen A, Backman JT, Peczynski C, Kroger N, et al. Use of busulfan in conditioning for allogeneic hematopoietic stem cell transplantation in adults: a survey by the Transplant Complications Working Party of the EBMT. Bone Marrow Transpl. 2019;54(12):2013–9. https://doi.org/10.1038/s41409-019-0579-0
60 Fakhoury M, Jacqz-Aigrain E; pour le groupe Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et Thérapeutique; Médard Y, de Beaumais T. Suivi thérapeutique pharmacologique des 6-thioguanine nucléotides dans les leucémies aigues lymphoblastiques de l'enfant: intérêt et limites. Therapie. 2010;65(3):187–93. https://doi.org/10.2515/therapie/2010031
61 Jourdil N, Fonrose X, Boulieu R, Stanke-Labesque F; Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Suivi thérapeutique pharmacologique des 6-thioguanine nucléotides dans les maladies inflammatoires cryptogéniques de l'intestin: intérêt et limites. Therapie. 2010;65(3): 177–86. https://doi.org/10.2515/therapie/2010030
62 McLeod HL, Krynetski EY, Relling MV, Evans WE. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. Leukemia. 2000;14(4):567–72. https://doi.org/10.1038/sj.leu.2401723
63 Relling MV, Hancock ML, Rivera GK, Sandlund JT, Ribeiro RC, Krynetski EY, et al. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. J Natl Cancer Inst. 1999;91(23):2001–8. https://doi.org/10.1093/jnci/91.23.2001
64 Dervieux T, Meyer G, Barham R, Matsutani M, Barry M, Boulieu R, et al. Liquid chromatography-tandem mass spectrometry analysis of erythrocyte thiopurine nucleotides and effect of thiopurine methyltransferase gene variants on these metabolites in patients receiving azathioprine/6-mercaptopurine therapy. Clin Chem. 2005;51(11):2074–84. https://doi.org/10.1373/clinchem.2005.050831
65 Cuffari C, Hunt S, Bayless T. Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. Gut. 2001; 48(5):642–6. https://doi.org/10.1136/gut.48.5.642
66 Derijks LJ, Gilissen LP, Hooymans PM, Hommes DW. Review article: thiopurines in inflammatory bowel disease. Aliment Pharmacol Ther. 2006;24(5):715–29. https://doi.org/10.1111/j.1365-2036.2006.02980.x
67 Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Theoret Y, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology. 2000; 118(4):705–13. https://doi.org/10.1016/s0016-5085(00)70140-5
68 Anthony M, Berg MJ. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: Part I. J Womens Health Gend Based Med. 2002;11(7):601–15. https://doi.org/10.1089/152460902760360559
69 Klemetsdal B, Flaegstad T, Aarbakke J. Is there a gender difference in red blood cell thiopurine methyltransferase activity in healthy children? Med Pediatr Oncol. 1995; 25(6):445–9. https://doi.org/10.1002/mpo.2950250605
70 Lilleyman JS, Lennard L, Rees CA, Morgan G, Maddocks JL. Childhood lymphoblastic leukaemia: sex difference in 6-mercaptopurine utilization. Br J Cancer. 1984;49(6):703–7. https://doi.org/10.1038/bjc.1984.111
71 Hale JP, Lilleyman JS. Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. Arch Dis Child. 1991;66(4):462–6. https://doi.org/10.1136/adc.66.4.462
72 Szumlanski CL, Honchel R, Scott MC, Weinshilboum RM. Human liver thiopurine methyltransferase pharmacogenetics: biochemical properties, liver-erythrocyte correlation and presence of isozymes. Pharmacogenetics. 1992;2(4):148–59. https://doi.org/10.1097/00008571-199208000-00002
73 Serpe L, Calvo PL, Muntoni E, D'Antico S, Giaccone M, Avagnina A, et al. Thiopurine S-methyltransferase pharmacogenetics in a large-scale healthy Italian-Caucasian population: differences in enzyme activity. Pharmacogenomics. 2009;10(11):1753–65. https://doi.org/10.2217/pgs.09.103
74 Uppugunduri CR, Ansari M. Influence of age, sex, and haplotypes of thiopurine methyltransferase (TPMT) gene on 6- mercaptopurine toxicity in children with acute lymphoblastic leukemia. Eur J Clin Pharmacol. 2012;68(5):887–6. https://doi.org/10.1007/s00228-011-1185-2
75 Lee JJ, Beumer JH, Chu E. Therapeutic drug monitoring of 5-fluorouracil. Cancer Chemother Pharmacol. 2016;78(3):447–64. https://doi.org/10.1007/s00280-016-3054-2
76 Gamelin EC, Danquechin-Dorval EM, Dumesnil YF, Maillart PJ, Goudier MJ, Burtin PC, et al. Relationship between 5-fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. Cancer. 1996;77(3):441–51. https://doi.org/10.1002/(SICI)1097-0142(19960201)77:3<441::AID-CNCR4>3.0.CO;2-N
77 Gamelin E, Boisdron-Celle M, Delva R, Regimbeau C, Cailleux PE, Alleaume C, et al. Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin: results of a multicentric prospective trial of fluorouracil dosage optimization by pharmacokinetic monitoring in 152 patients. J Clin Oncol. 1998;16(4):1470–8. https://doi.org/10.1200/JCO.1998.16.4.1470
78 Kaldate RR, Haregewoin A, Grier CE, Hamilton SA, McLeod HL. Modeling the 5-fluorouracil area under the curve versus dose relationship to develop a pharmacokinetic dosing algorithm for colorectal cancer patients receiving FOLFOX6. Oncologist. 2012; 17(3):296–302. https://doi.org/10.1634/theoncologist.2011-0357
79 Gamelin E, Delva R, Jacob J, Merrouche Y, Raoul JL, Pezet D, et al. Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(13): 2099–105. https://doi.org/10.1200/JCO.2007.13.3934
80 https://www.ema.europa.eu/en/documents/press-release/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine_en.pdf
81 Loriot MA, Ciccolini J, Thomas F, Barin-Le-Guellec C, Royer B, Milano G, 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. 2018;105(4):397–407. https://doi.org/10.1016/j.bulcan.2018.02.001
82 Bressolle F, Joulia JM, Pinguet F, Ychou M, Astre C, Duffour J, et al. Circadian rhythm of 5-fluorouracil population pharmacokinetics in patients with metastatic colorectal cancer. Cancer Chemother Pharmacol. 1999;44(4): 295–302. https://doi.org/10.1007/s002800050980
83 Toffoli G, Corona G, Sorio R, Robieux I, Basso B, Colussi AM, et al. Population pharmacokinetics and pharmacodynamics of oral etoposide. Br J Clin Pharmacol. 2001; 52(5):511–9. https://doi.org/10.1046/j.0306-5251.2001.01468.x
84 Moeung S, Chevreau C, Marsili S, Massart C, Flechon A, Delva R, et al. Pharmacokinetic and pharmacogenetic study of etoposide in high-dose protocol (TI-CE) for advanced germ cell tumors. Pharm Res. 2020;37(7):147. https://doi.org/10.1007/s11095-020-02861-5

85 Barnett S, Errington J, Sludden J, Jamieson D, Poinsignon V, Paci A, et al. Pharmacokinetics and pharmacogenetics of cyclophosphamide in a neonate and infant childhood cancer patient population. Pharmaceuticals. 2021;14(3):272. https://doi.org/10.3390/ph14030272
86 Salinger DH, McCune JS, Ren AG, Shen DD, Slattery JT, Phillips B, et al. Real-time dose adjustment of cyclophosphamide in a preparative regimen for hematopoietic cell transplant: a Bayesian pharmacokinetic approach. Clin Cancer Res. 2006;12(16):4888–98. https://doi.org/10.1158/1078-0432.CCR-05-2079
87 Kerbusch T, de Kraker J, Mathjt RA, Beijnen JH. Population pharmacokinetics of ifosfamide and its dechloroethylated and hydroxylated metabolites in children with malignant disease: a sparse sampling approach. Clin Pharmacokinet. 2001;40(8):615–25. https://doi.org/10.2165/00003088-200140080-00005
88 Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10:337. https://doi.org/10.1186/1471-2407-10-337
89 El-Demerdash E, Ali AA, El-Taher DE, Hamada FM. Effect of low-protein diet on anthracycline pharmacokinetics and cardiotoxicity. J Pharm Pharmacol. 2012;64(3):344–52. https://doi.org/10.1111/j.2042-7158.2011.01413.x
90 Decosterd LA, Widmer N, André P, Aouri M, Buclin T. The emerging role of multiplex tandem mass spectrometry analysis for therapeutic drug monitoring and personalized medicine. Trends Anal Chem. 2016;84:5–13. https://doi.org/10.1016/j.trac.2016.03.019
91 Palmer J, McCune JS, Perales MA, Marks D, Bubalo J, Mohty M, et al. Personalizing busulfan-based conditioning: considerations from the American society for blood and marrow transplantation practice guidelines committee. Biol Blood Marrow Transpl. 2016;22(11):1915–25. https://doi.org/10.1016/j.bbmt.2016.07.013
92 http://www.nanotera.ch/projects/368.php
93 Dubovitskaya A, Buclin T, Schumacher M, Aberer K, Thoma Y. TUCUXI—an intelligent system for personalized medicine: from individualization of treatments to research databases and back. Acm-bcb' 2017: proceedings of the 8th acm international conference on bioinformatics, computational biology, and health informatics. New York, NY, USA: Association for Computing Machinery; 2017. p. 223–32.
94 Goutelle S, Thoma Y, Buffet R, Philippe M, Buclin T, Guidi M, et al. Implementation and cross-validation of a pharmacokinetic model for precision dosing of busulfan in hematopoietic stem cell transplanted children. Pharmaceutics. 2022;14(10):2107. https://doi.org/10.3390/pharmaceutics14102107
95 Taddeo A, Prim D, Bojescu ED, Segura JM, Pfeifer ME. Point-of-Care therapeutic drug monitoring for precision dosing of immunosuppressive drugs. J Appl Lab Med. 2020;5(4):738–61. https://doi.org/10.1093/jalm/jfaa067
96 Rodino F, Bartoli M, Carrara S. Simultaneous and selective detection of etoposide and methotrexate with single electrochemical sensors for therapeutic drug monitoring. IEEE Sens Lett. 2023;7(8):1–4. https://doi.org/10.1109/lsens.2023.3300817
97 Zouari M, Barderas R, Pingarrón JM, Raouafi N, Campuzano S. First electrochemical bioplatform to assist in personalized 5-fluorouracil chemotherapy. Sensor Actuator B Chem. 2024;401:135017. https://doi.org/10.1016/j.snb.2023.135017
98 Baj-Rossi C, De Micheli G, Carrara S. Electrochemical detection of anti-breast-cancer agents in human serum by cytochrome P450-coated carbon nanotubes. Sensors. 2012;12(5):6520–37. https://doi.org/10.3390/s120506520