THERAPEUTIC ADVANCES in
Medical Oncology

Systematic Review

Therapeutic drug monitoring guidelines in oncology: what do we know and how to move forward? Insights from a systematic review

Ther Adv Med Oncol

2024, Vol. 16: 1–16

DOI: 10.1177/17588359241250130

Xinya Li*, Zaiwei Song*, Zhanmiao Yi*, Jiguang Qin, Dan Jiang, Zhitong Wang, Huibo Li and Rongsheng Zhao

Abstract

Background: Compared with anti-infective drugs, immunosuppressants and other fields, the application of therapeutic drug monitoring (TDM) in oncology is somewhat limited.

Objective: We aimed to provide a comprehensive understanding of TDM guidelines for antineoplastic drugs and to promote the development of individualized drug therapy in oncology.

Design: This study type is a systematic review.

Data sources and methods: This study was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. Databases including PubMed, Embase, the official websites of TDM-related associations and Chinese databases were comprehensively searched up to March 2023. Two investigators independently screened the literature and extracted data. The methodological and reporting quality was evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) and the Reporting Items for Practice Guidelines in Healthcare (RIGHT), respectively. Recommendations and quality evaluation results were presented by visual plots. This study was registered in PROSPERO (No. CRD42022325661).

Results: A total of eight studies were included, with publication years ranging from 2014 to 2022. From the perspective of guideline development, two guidelines were developed using evidence-based methods. Among the included guidelines, four guidelines were for cytotoxic antineoplastic drugs, three for small molecule kinase inhibitors, and one for antineoplastic biosimilars. Currently available guidelines and clinical practice provided recommendations of individualized medication in oncology based on TDM, as well as influencing factors. With regard to methodological quality based on AGREE II, the average overall quality score was 55.21%. As for the reporting quality by RIGHT evaluation, the average reporting rate was 53.57%.

Conclusion: From the perspective of current guidelines, TDM in oncology is now being expanded from cytotoxic antineoplastic drugs to newer targeted treatments. Whereas, the types of antineoplastic drugs involved are still small, and there is still room for quality improvement. Furthermore, the reflected gaps warrant future studies into the exposure–response relationships and population pharmacokinetics models.

Keywords: antineoplastic drugs, systematic review, the Appraisal of Guidelines for Research and Evaluation II, therapeutic drug monitoring, the Reporting Items for Practice Guidelines in Healthcare

Received: 23 November 2023; revised manuscript accepted: 9 April 2024.

Correspondence to:
Rongsheng Zhao
Department of Pharmacy, Peking University Third Hospital, 49 North Garden Road, Haidian District, Beijing 100191, China

Institute for Drug Evaluation, Peking University Health Science Center, Beijing, China

Therapeutic Drug Monitoring and Clinical Toxicology Center, Peking University, Beijing, China
zhaorongsheng@bjmu.edu.cn

Xinya Li
Jiguang Qin
Dan Jiang
Department of Pharmacy, Peking University Third Hospital, Beijing, China

Institute for Drug Evaluation, Peking University Health Science Center, Beijing, China

Therapeutic Drug Monitoring and Clinical Toxicology Center, Peking University, Beijing, China

Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, China

Zaiwei Song
Zhanmiao Yi
Zhitong Wang
Department of Pharmacy, Peking University Third Hospital, Beijing, China

Institute for Drug Evaluation, Peking University Health Science Center, Beijing, China

Therapeutic Drug Monitoring and Clinical Toxicology Center, Peking University, Beijing, China

Huibo Li
School of Pharmacy, Faculty of Medicine, Macau University of Science and Technology, Macau SAR, China

Department of Pharmacy, Peking University Third Hospital, Beijing, China

Institute for Drug Evaluation, Peking University Health Science Center, Beijing, China

Therapeutic Drug Monitoring and Clinical Toxicology Center, Peking University, Beijing, China

*These authors contributed equally.

Introduction

Therapeutic drug monitoring (TDM) refers to the clinical practice of measuring drug exposure at designated intervals to tailor drug doses, thereby optimizing outcomes in individual patients.[1] The past decades have witnessed dramatic progress in the field of TDM. At present, TDM is broadly applied to anti-infective drugs, immunosuppressive drugs, nervous system diseases, inflammatory bowel diseases and other areas, promoting the development of individualized therapy. In multiple clinical scenarios, TDM-based dose individualization strategies have been shown to significantly improve health outcomes, including improved effectiveness, shorter hospitalization, and reduced side effects.[2–6]

Population pharmacokinetics (PopPK) modeling and simulation can aid in optimizing TDM in multiple ways.[7] In turn, TDM is of great significance for translating the PopPK model into clinical practice.[8] In individualized therapy of antineoplastic drugs, taking busulfan as an example, a PopPK model for busulfan is now available in a software, and the TDM of busulfan has been recommended to be implemented together.[9–11] However, compared with anti-infective drugs and other areas, the TDM of antineoplastic drugs is conducted less from both the variety of drugs and the scope of implementation.[8,12] In contrast, the TDM of anti-infectives such as vancomycin and voriconazole has been well implemented in many countries worldwide since a series of TDM guidelines and dose calculators using PopPK models have been developed and applied.[13–16]

The effectiveness and safety management of antineoplastic drugs is always a major problem in clinical practice.[17] Highly diversified interindividual pharmacokinetic (PK) profiles always result in supratherapeutic or subtherapeutic concentrations of antineoplastic drugs.[1] Inadequate doses can have an impact on treatment failure, which undoubtedly leads to a poor prognosis and even increases cancer mortality.[18] On the other hand, the overdose may cause prominent toxicity. According to the latest statistics in China, antineoplastic drugs accounted for the largest number of serious adverse drug reactions/events in 2021 (33.2%), surpassing anti-infectives (28.1%). Regarding the proportion of serious reports in each category of drugs, antineoplastic drugs were the highest (43.0%).[19] In addition, global expenditure for oncology drugs is substantial, accounting for the largest spending of any specialty in recent years.[20] Against this backdrop, the rational use of TDM in oncology has high potential to help improve clinical outcomes and reduce costs.

From the perspective of evidence-based medicine (EBM), guidelines are considered as the highest level of evidence.[21] Guidelines help to promote the transformation of clinical practice by building a bridge between research evidence and clinical practice. In recent years, guidelines on the TDM of antineoplastic drugs have been developed successively to support the TDM implementation in oncology. However, the following questions remain to be answered: (a) What do the available TDM guidelines in antineoplastic drugs cover? (b) How is the quality of these guidelines? (c) How can TDM guidelines for antineoplastic drugs be better developed and applied?

Herein, this systematic review aims to provide a comprehensive understanding of the overall situation and current recommendations as well as the quality evaluation of TDM guidelines in oncology and to promote the development of TDM in the field of oncology.

Materials and methods

This study was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Supplemental File I).[22] We registered this study on PROSPERO (CRD42022325661) (Supplemental File II). The registration encompasses a broader scope unrestricted in types of diseases and drugs, with our current study specifically focusing on the field of oncology.

Search strategy and study selection

PubMed, Embase, China National Knowledge Infrastructure, Wanfang Data, and Chinese biomedical literature service system as well as the official websites of TDM-related associations and drug regulatory agencies (including drug labels) were comprehensively searched. The search period was from inception to 17th March 2023. Keywords related to therapeutic drug monitoring (drug monitoring, drug concentration, drug level, concentration monitoring, TDM, therapeutic monitoring, dose optimization, pharmacovigilance) and guidelines (guideline, guidance, guide, consensus, recommendation, standard, statement, handbook, organization and administration, management

service organizations, and practice management) as well as MeSH terms (Drug Monitoring, Pharmacovigilance, Guideline, Guidance, Guide, Consensus, and Standard of Care) were used to identify TDM guidelines in the search (Table S1 in Supplemental File III). TDM guidelines in oncology were further identified by manual screening.

Study selection

Two authors independently screened and selected potentially eligible studies from the search results, first through titles and abstracts and then full texts. The inclusion criteria were as follows: guidelines, guidance, guide, consensus, recommendations, standards, scientific statements, position statements, and position papers related to TDM of antineoplastic drugs, including management and/or technical recommendations. The exclusion criteria were as follows: (a) study design including clinical research, animal experiment or cell experiment; (b) translated and excerpt guidelines, guideline development protocol, and guideline interpretation; (c) studies not published in Chinese or English. Any disagreement was discussed and reconciled by the corresponding researcher.

Data extraction

Data extraction was carried out by two authors independently. The following data was extracted based on a predesigned standardized extraction form: (a) basic characteristics: title, first author, year, country, development organization, publication type, journal, number of references, and drugs; (b) contents: targeting people, TDM-related recommendations (indications, sampling time, monitoring method, monitoring indicator, therapeutic window, dose regimens, dose adjustment basis, influencing factors, etc.), and covering outcome (efficacy, safety, economics, and compliance).

Quality evaluation

The methodological and reporting quality were rated by two authors independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II and Reporting Items for Practice Guidelines in Healthcare (RIGHT), respectively. The AGREE II instrument consists of 23 items from 6 domains, and the assessment was performed as a two-step process. First, each item was scored on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree), depending on the completeness and quality of reporting. Second, the score of each domain was calculated by summing all the scores of the single items in the domain and by scaling the total points as a per-centage of the maximum possible score for each domain. The scaled domain score was calculated as (obtained score − minimum possible score)/(maximum score − minimum possible score).[23,24] The RIGHT checklist consists of 22 items from 7 domains. Each item is rated as 'yes', 'no', or 'unclear' based on whether the guidelines report the re-quired information.[25]

Statistical analysis

Data were extracted and recorded in Microsoft Office Excel 2019 software (Microsoft Corp.) by two investigators and subsequently checked by another investigator. Descriptive statistical analysis was conducted using Microsoft Office Excel 2019 software (Microsoft Corp.). Qualitative variables were presented as numbers and percentages. For the results of methodological quality based on AGREE II, an average mark was given for each domain score from the scores of the two appraisers, and the final score was calculated as a percentage. For the results of reporting quality based on RIGHT, the average reporting rate was calculated for each item and then for each domain. Recommendations and quality evaluation results of guidelines were presented by visual plots.[26]

Results

Study selection and characteristics of the included studies

Eight studies were included, all of which were technical guidelines with publication years ranging from 2014 to 2021.[27–34] Stratified by publication country, the United States of America, Netherlands, and China published two guidelines each, followed by the United Kingdom and Switzerland (one each). There are two guidelines developed by international organizations, which are both the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT).[30,33] According to the publication type indicated by the author, there are recommendations,[29–31] practical guidelines,[27] practice guideline,[34] diagnostics guidance,[28] consensus guidelines,[33] and consensus.[32] From the perspective of formulation methods, the Division

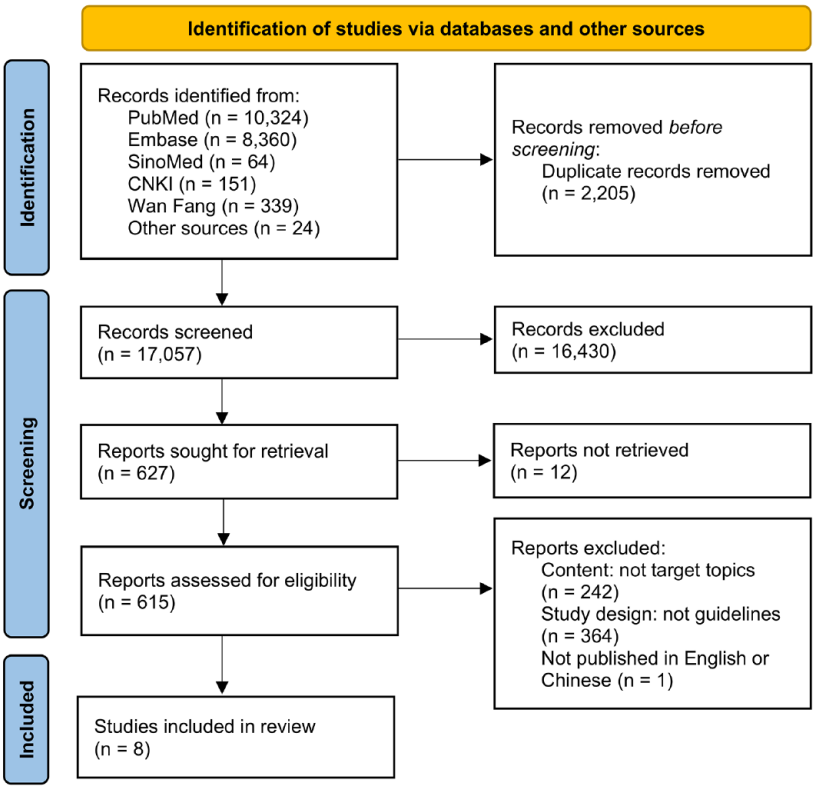

Figure 1. The PRISMA 2020 flow diagram of study selection for the systematic review.
PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of Therapeutic Drug Monitoring, Chinese Pharmacological Society (CHINA-TDM) 2022 and National Institute for Health and Care Excellence (NICE) 2014 are evidence-based. The targeted population of all the guidelines included healthcare professionals such as doctors and pharmacists, but only one included patients.[34] All of the guidelines covered effectiveness and safety, with four covering economics[28,31,32,34] and none covering compliance (Figure 1 and Table 1).

Methodological quality evaluation of AGREE II

The average score of overall quality was 55.21%. For 'I would recommend this guideline for use', all guidelines were rated as 'recommended', among which the Netherlands Cancer Institute (NKI) 2014 was rated as 'with modifications' (Figure 2; Table S2 in Supplemental File III).

Among the six domains of AGREE II, scope and purpose received the highest score (87.30%). All guidelines clearly described the overall purpose of the guidelines and their coverage of health issues. However, these guidelines scored relatively low for the applicable population (patients, the public, etc.). In terms of stakeholder involvement, the average score was 38.10%. Some guideline development groups did not include methodologists or pharmacologists. Six guidelines did not collect the views and preferences of the target population. More than half of the guidelines did not clearly define the target users. For rigor of development, the average score was 32.29%. Most guidelines did not describe the search method (including search database, search time, search terms, etc.), inclusion and exclusion criteria, strength of evidence, and method of forming recommendations. In the domain of clarity of presentation, the score was 53.57%. For most guidelines, the recommendations were clear, and the important recommendations were easy to identify. In terms of applicability, the average score was 38.39%. The monitoring or auditing standards of the guidelines were clear, but less consideration was given to the tools and potentially relevant resources for applying the recommendations. In the domain of editorial independence, the average

Table 1. Basic information and recommendations of included therapeutic drug monitoring guidelines in oncology.

No.	First author	Year	Country	Development organization	Publication type	Drugs	Indications	Sampling time	Monitoring method	Monitoring indicator	Therapeutic window	Dose adjustment basis
1	Huixin Yu[27]	2014	Netherlands	NKI	Practical guidelines	Tyrosine kinase inhibitors	Not available	Not available	Not available	C_{min}, C_{max}, AUC	See the guideline for details	Not available
2	NICE[28]	2014	the United Kingdom	NICE	Diagnostics guidance	5-FU	Having continuous fluorouracil infusion	At least 18 h after the start of the infusion	the My5-FU assay, HPLC, LC–MS	AUC	AUC 16–24 mg·h/L	PK
3	Remy B. Verheijen[29]	2017	Netherlands	NKI	Recommendations	Kinase inhibitors	Not available	Not available	Not available	C_{min}, AUC	See the guideline for details	PK
4	Jan H. Beumer[30]	2019	the USA	IATDMCT	Recommendations	5-FU	Colorectal or head-and-neck cancer patients treated with 5-FU	On day 2 of a 48-h 5-FU infusion	HPLC or LC–MS/MS, nanoparticle-based immunoassay	AUC	AUC 20–30 mg×h/L[a]	Not available
5	Seid Hamzic [31]	2020	Switzerland	SPT	Recommendations	Fluoropyrimidines	Treated with various 5-FU treatment regimens	Sufficient time prior to the end of infusion (e.g. after 24–36 h for 48-h infusions), avoid an early blood draw close to the start	HPLC–MS	AUC	For continuous 5-FU infusion, AUC 20–30 mg×h/L[a]	Experience
6	CNPHARS and CJFH[32]	2020	China	CNPHARS, CJFH	Consensus	Antineoplastic biosimilars	Received antineoplastic biosimilars	Not available	LC–MS, immunoassay	AUC, C_{ss}	Not available	Not available
7	William A. Clarke[33]	2021	the USA	IATDMCT	Consensus guidelines	Imatinib	CML or GIST patients treated imatinib	Before next dose, after steady state concentration achieved, which takes 5–7 days	Not available	C_{max}, C_{min}, AUC	CML, C_{min} ⩾1000 ng/mL; GIST, C_{min} ⩾1100 ng/mL	Not available
8	Zaiwei Song[34]	2022	China	CHINA-TDM	Practice guideline	Methotrexate	Hematological malignancy or osteosarcoma patients treated with HDMTX	At least 24 h, 48 h, and 72 h after the 24 h infusion start, until the concentration is below 0.1–0.2 μmol/L[b]	Chromatography-related methods	$C_{4-6\,h}$, $C_{24\,h}$, $C_{48\,h}$, $C_{72\,h}$, Css	See the guideline for details	PK

[a]Not appropriate for 5-FU bolus dosing and infusions of 120 h and longer.
[b]When elimination delay, acute kidney injury, or other serious adverse reactions occur, the monitoring interval should be shortened, and the frequency should be increased.
5-FU, 5-fluorouracil; AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration; C_{min}, trough plasma concentration; C_{ss}, steady-state plasma concentration; $C_{4-6\,h}$, plasma concentration at the end of 4–6 h infusion; $C_{24\,h}$, plasma concentration at 24 h; $C_{48\,h}$, plasma concentration at 48 h; $C_{72\,h}$, plasma concentration at 72 h; CJFH, China-Japan Friendship Hospital; CML, chronic myeloid leukemia; CNPHARS, Chinese Pharmacological Society; GIST, gastrointestinal stromal tumor; HDMTX, high-dose methotrexate; HPLC, high-performance liquid chromatography; IATDMCT, International Association of Therapeutic Drug Monitoring and Clinical Toxicology; LC–MS, liquid chromatography–mass spectrometry; MS, mass spectrometry; NICE, National Institute for Health and Care Excellence; NKI, Netherlands Cancer Institute; PK, pharmacokinetics; SPT, the Swiss Group of Pharmacogenomics and Personalized Therapy.

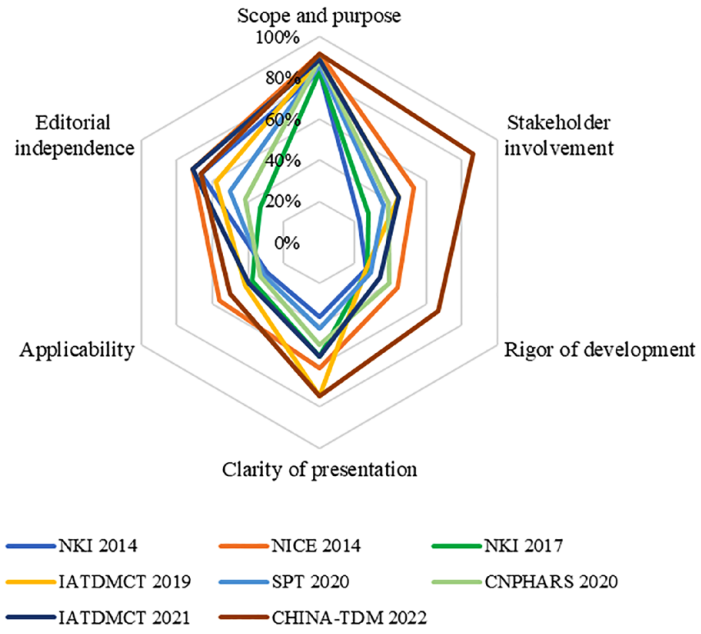

Figure 2. Methodological quality of included guidelines according to the AGREE II instrument.
AGREE, Appraisal of Guidelines for Research and Evaluation; CHINA-TDM, The Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society; CNPHARS, Chinese Pharmacological Society; IATDMCT, International Association of Therapeutic Drug Monitoring and Clinical Toxicology; NICE, National Institute for Health and Care Excellence; NKI, Netherlands Cancer Institute; SPT, the Swiss Group of Pharmacogenomics and Personalized Therapy.

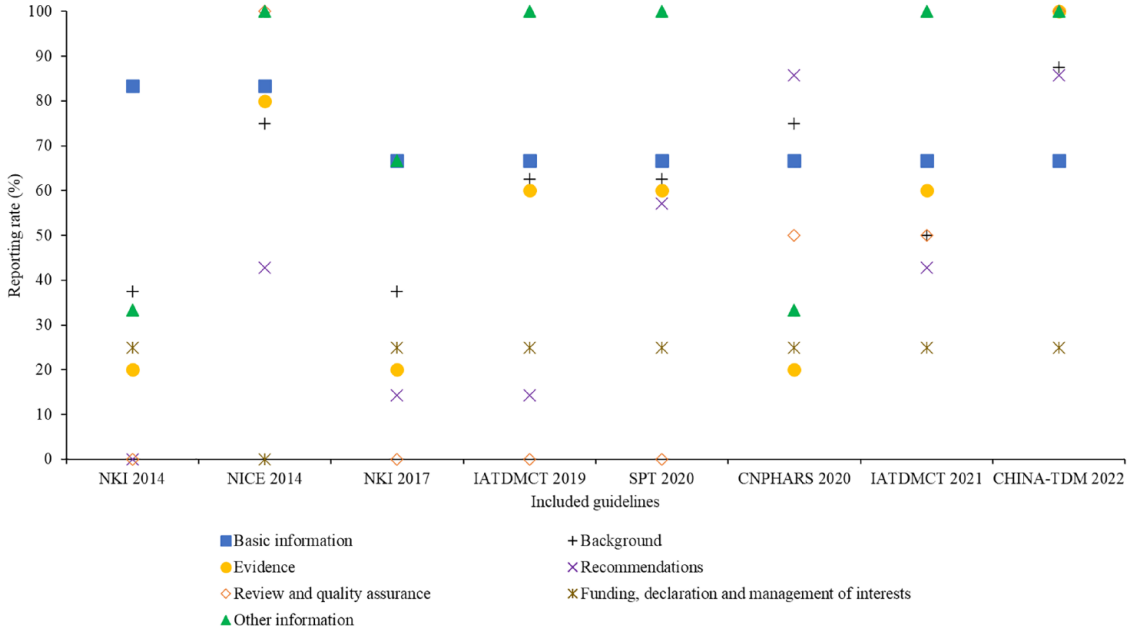

Figure 3. Reporting quality of included guidelines according to the RIGHT checklist.
RIGHT, Reporting Items for Practice Guidelines in Healthcare.

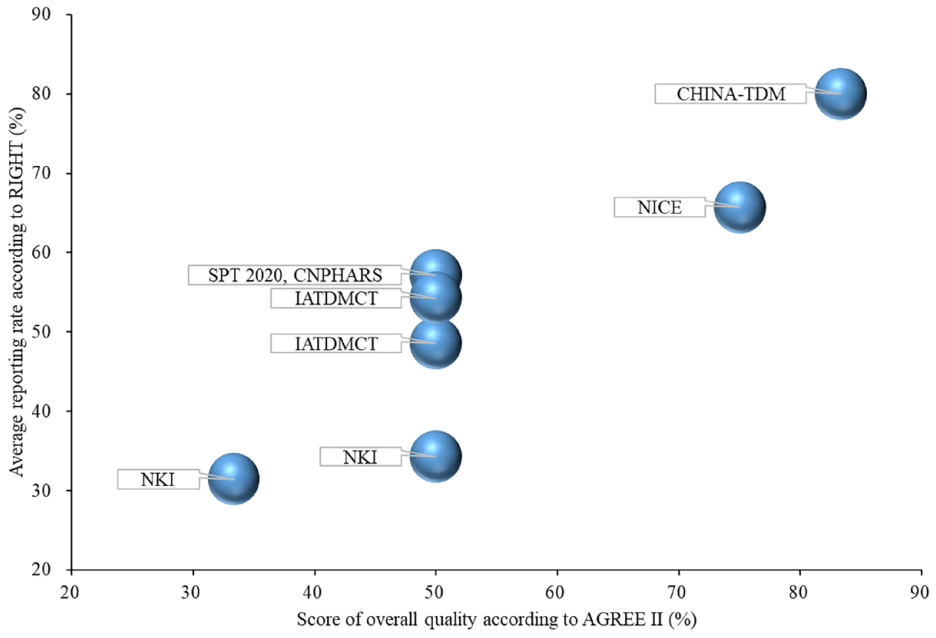

Figure 4. Comprehensive analysis of methodological and reporting quality of included guidelines.
AGREE II, the Appraisal of Guidelines for Research and Evaluation II; RIGHT, the Reporting Items for Practice Guidelines in Healthcare.

score was 55.95%. The guidelines all mentioned the conflict of interest of guideline development group members, but the description of the influence of sponsors on the guidelines, the types of conflict of interest, the collection methodology, and the influence on the development process of the guidelines and the formation of recommendations was not clear enough.

Reporting quality evaluation of RIGHT

Among the seven domains of RIGHT, the domain of other information received the highest reporting rate (Figure 3; Table S3 in Supplemental File III). The reporting rate of other information (including access, evidence gaps, and limitations) was 79.17%. In terms of basic information, most guidelines satisfied the reporting standards, with an average reporting rate of 70.83%. Defining new or key terms and providing a list of abbreviations and acronyms was not applicable for these guidelines. In terms of background, guidelines performed better in brief description of the health problem(s) (100.00%), aim(s) of the guideline and specific objectives (100.00%) and target populations (Standard *a* 100.00%, Standard *b* 25.00%) than end users and settings (Standard *a* 50.00%, Standard *b* 0.00%), which was not clearly expressed. In terms of evidence, most guidelines met the standards of health care questions (Standard *a* 100.00%, Standard *b* 25.00%) and systematic reviews (62.50%), but only CHINA-TDM 2021 conducted assessment of the certainty of the body of evidence (12.50%). In terms of recommendations (42.86%) and reviews and quality assurance (37.5), relatively fewer guidelines met the criteria. In terms of funding and declaration and management of interests, most guidelines report these contents incompletely, with an average reporting rate of 21.88%.

Combining the methodological and reporting quality evaluation, CHINA-TDM 2022 performed best, followed by NICE 2014, and NKI 2014 received the lowest score (Figure 4).

Scope of included guidelines

Cytotoxic antineoplastic drugs. Conventional cytotoxic antineoplastic drugs are poorly specific cell poisons characterized by a narrow window of maneuver. Although significant efforts have been invested in recent decades in TDM research to explore the relationship between drug exposure and the response achieved for therapeutic efficacy as well as drug toxicity for cytotoxic antineoplastic drugs, high-level evidence is lacking.[35] Currently, TDM has been implemented in

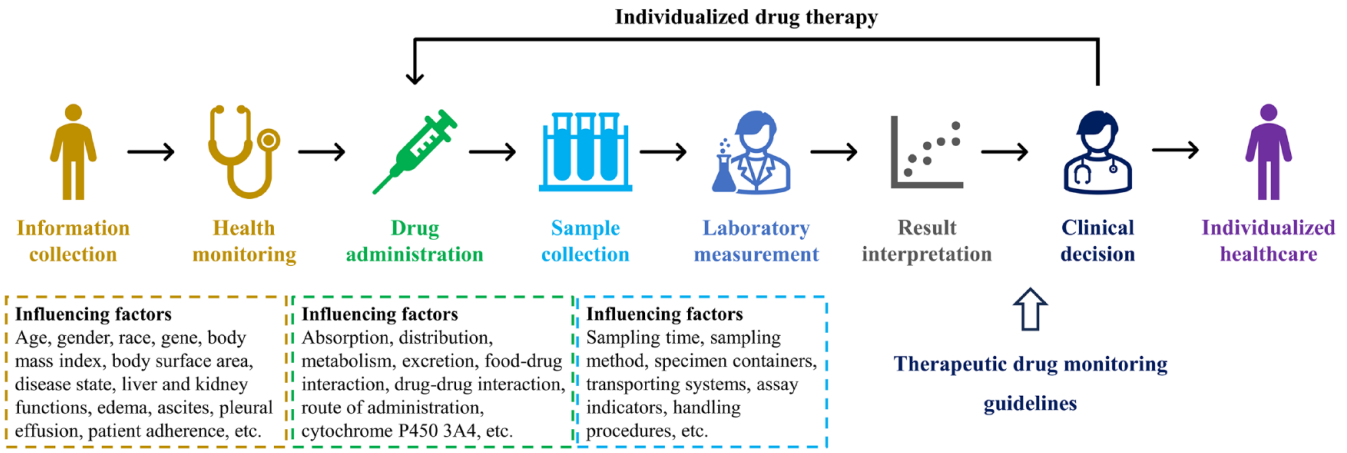

Figure 5. The workflow of individualized therapy of antineoplastic drugs based on therapeutic drug monitoring.

individualized therapy of 5-fluorouracil (5-FU), methotrexate, paclitaxel, docetaxel, busulfan, and etoposide. However, in our search, four guidelines were developed for the TDM of cytotoxic antineoplastic drugs, including 5-FU and methotrexate. In the official labels of methotrexate and busulfan, it is recommended that TDM should be conducted to guide the management of adverse events.

As a diagnostics guidance, NICE 2014 concluded that it was not appropriate to consider the My5-FU assay equivalent to high-performance liquid chromatography and liquid chromatography–mass spectrometry to determine plasma levels of 5-FU and guide dose adjustment in clinical practice, which introduced uncertainty into the interpretation of effectiveness, safety, and economy evaluation.[28] IATDMCT 2019 summarized the data on TDM of 5-FU therapy and concluded that TDM is strongly recommended in patients receiving common 5-FU dosing regimens.[30] In the guidelines developed by the Swiss Group of Pharmacogenomics and Personalized Therapy, it was recommended to implement individualized fluoropyrimidine chemotherapy combining genotype and TDM.[31]

CHINA-TDM 2022 provided an evidence-based practice guideline on medication therapy of high-dose methotrexate, including evaluation prior to administration, routine dosing regimen, TDM, leucovorin rescue and management of toxicities.[34] In the label of the methotrexate injection, it is recommended that serum concentrations of methotrexate should be monitored closely to guide leucovorin or levoleucovorin therapy. Moreover, a recently updated National Comprehensive Cancer Network clinical practice guidelines in oncology recommended the use of MTXPK.org, an online PK tool designed to help clinicians understand the PKs of high-dose methotrexate, especially with regard to delayed clearance.[36]

Small molecule kinase inhibitors. Small molecule kinase inhibitors (KIs) have contributed substantially to improved survival outcomes in patients with advanced disease. Further to this, there has been a building body of evidence that the benefit derived from these drugs may be further enhanced by individualizing dosing based on TDM. Among 77 approved KIs, relationships between exposure-response and exposure-toxicity have been established in 26 drugs and 46 ones, respectively.[37] However, only three guidelines were developed for TDM of small molecule KIs.

NKI 2014 presented a practical guideline of TDM for tyrosine kinase inhibitors (TKIs), focusing on the exposure and response relationships of TKIs with proposed PK targets and the PK targets for dose titrations.[27] Aiming to integrate the available clinical PK and pharmacodynamics (PD) data into practical recommendations that can be used to personalize treatment with KIs, TDM recommendations for 12 drugs were provided in NKI 2017.[29] For imatinib, the IATDMCT summarized the scientific evidence to develop a consensus guideline, which is useful to minimize PK variability, improve efficacy and assess adherence to imatinib therapy.[33]

Not only is there a gap between evidence and guidelines, but also between guidelines and

practice. TDM of small molecule KIs has not yet been performed routinely in the standard care of oncology patients up to now. Additionally, although dried blood microsamples are minimally invasive and considered convenient and simple, there is no related method used for TDM in routine yet.[38] TDM for KIs should be approached on a case-by-case basis, taking into account the specific characteristics of each agent and the individual patient's needs.

Monoclonal antibodies. In recent decades, therapeutic monoclonal antibodies have been approved for the market and successively put into clinical application, which improves not only the effectiveness of tumor treatment but also the accessibility of antineoplastic drugs. However, due to pharmacological complexity and individual variability, TDM helps to promote the rational application of therapeutic antibodies. It is worth mentioning that developing accurate, efficient, convenient, economical, and standardized monitoring methods is a challenge that needs to be addressed in clinical settings.

Biosimilars, while approved based on similarity to their reference products, may still undergo rigorous post-market surveillance to ensure their safety and efficacy in real-world settings in some countries and regions. To give full play to pharmacists' pharmaceutical technology supporting their role in clinical drug use and ensure maximum benefits for patients, the Pharmaceutical Expert Consensus on the Therapeutic Drug Monitoring of Antitumor Biosimilars (2020 edition) focused on the TDM of antineoplastic biosimilars to solve the clinical treatment problems based on the existing evidence and provided recommendations for clinicians and pharmacists at all levels of medical institutions.[32] Probably, as the body of evidence grows, the concerns surrounding antineoplastic biosimilars will gradually dissipate, allowing for their widespread adoption and utilization in the treatment of cancer.

Recommendations and workflow on the implementation of TDM

For recommendations of TDM, six guidelines reported indications and recommended implementing TDM routinely. A total of five guidelines reported sampling time, which varied among drugs. With respect to monitoring methods, chromatography-related analytical methods were mostly recommended, with five guidelines reporting on them. All guidelines reported the monitoring indicator, and AUC was recommended by most guidelines. Therapeutic window was reported by seven guidelines, which was closely related to diseases and drugs. Four guidelines mentioned dose adjustment, among which three were PK/PD-based and one was experience-based (Table 1).

Available guidelines and clinical practice provided a common workflow of individualized antineoplastic drug administration based on TDM. In addition, many factors may influence the results of TDM, which can be classified as patient-related, drug-related, and operation-related. Before drug therapy, the health status of each patient needs to be evaluated comprehensively, based on which individualized drug therapy can be determined by a multidisciplinary team. It is worth mentioning that the administration mode and potential interaction need to be considered. After drug administration, TDM should be planned to assess drug exposure *in vivo*, based on which healthcare professionals can determine if medication regimen changes are needed. The disease status and health conditions of patients also need to be assessed during and after drug therapy. In the meantime, individualized care should be provided (Figure 5).

Discussion

In recent decades, rapid progress has been made in the field of TDM. However, the application of TDM in oncology is relatively limited.[39] Guidelines are of great significance for guiding and promoting clinical practice reform, whereas the current situation of TDM guidelines in antineoplastic drugs remains unclear. Herein, focusing on current guidelines, this systematic review aimed to provide an overall understanding of TDM in oncology from the perspective of evidence-based evaluation of guidelines. The scope and recommendations as well as the methodological and reporting quality of the guidelines were comprehensively summarized.

Scope and quality of available TDM guidelines in oncology

Scope and recommendations. In this study, the included guidelines covered cytotoxic antineoplastic drugs, KIs, and biosimilars, and comprehensively provided recommendations for the implementation of TDM. These guidelines

consistently recommended routine TDM for the antineoplastic drugs involved. For monitoring methods, due to good selectivity, sensitivity, and high throughput, chromatography-related analytical methods are most commonly recommended.[40] In the meantime, some new technical methods (e.g. immunoassays) are gradually being studied and applied.[41] Moreover, in real clinical practice, TDM is also implemented for other drugs not covered in available guidelines, such as docetaxel and paclitaxel. The slight gap indicates a lack of high-level evidence and the direction of future guideline development. Before developing guidelines, it is crucial to make a selection of drugs based on specific characteristics such as marked PK variability, concentration related therapeutic and adverse effects, narrow and defined target concentration range, potential serious adverse events, and a suitable and accessible laboratory assay.[1,6,8]

Methodological quality using AGREE II. The results of methodological quality using AGREE II showed that the average score of overall quality was moderate. Among the six domains, scope and purpose received the highest score, while rigor of development and stakeholder involvement received the lowest score. Systematic reviews of TDM guidelines for other types of drugs drew similar results.[42,43] As we can see, the methodological quality needs to be improved, especially in the domain of rigor of development and stakeholder involvement. It is worth mentioning that there is a tendency for the quality of the guidelines to increase over time. This is due in part to advances in the field of EBM and guideline methodology. The development and publication of the two quality evaluation tools may affect the availability of guideline development groups at the time and further affect the results of quality evaluation. In this study, all guidelines were published from 2014 to 2021, which was later than the release of the AGREE II instrument. Thus, all included guidelines could refer to this generic methodology in their development. However, the RIGHT statement was published in November 2016, which made it unlikely that earlier guidelines could refer to this RIGHT checklist.

Methodological quality using AGREE II. From the perspective of reporting quality using RIGHT, guidelines scored higher in basic information, background, and evidence but lower in recommendations, review and quality assurance and funding, declaration and management of interests. A previous review evaluated 48 National Comprehensive Cancer Network guidelines using the RIGHT statement and found that item 14 (rationale/explanation for recommendations), item 10b (indicate how the outcomes were selected and sorted) and item 12 (assessment of the certainty of the body of evidence) were notable deficiencies, which was in line with the results of our study.[44] Hence, more attention should be given to the reporting of evidence selection, recommendation formulation process, and level of evidence.

Development of TDM guidelines in oncology

Development methods. In this study, two guidelines adopted evidence-based methods, while the others were developed based on available literature and/or expert consensus. Obviously, evidence-based guidelines performed better in quality evaluation, which is consistent with previous findings.[43] With the development of guideline methodology, evidence-based clinical practice guidelines have been a tendency of guideline development. Hence, we strongly recommend the use of evidence-based methods in the development of TDM guidelines for cancer treatments.[45] Moreover, considering the limitations of available evidence in TDM, guidelines could clearly present the evidence gaps to provide directions for future research in the TDM of antineoplastic drugs.

In addition to using EBM methods, there is still room for improvement in methodological quality. First, it is recommended that guideline development groups include multidisciplinary experts involving different expertize and perspectives. Second, guideline development groups should collect the views and preferences of the target population and clearly define the target users. Third, the search method, inclusion and exclusion criteria, strength of evidence, and method of forming recommendations should be conducted scientifically and recorded comprehensively.[46]

Reporting recommendations. Several key points should also be noted in the full-text report of the guidelines after the guideline formulation. First, the process of guideline formulation needs to be clarified. Second, the role of funders in various stages of guideline development, dissemination, and implementation needs to be collected and presented. Third, authors should provide evaluation and management methods for conflicts of interest and access to declarations, which is also

in line with the requirements of AGREE II evaluation.[47] Fourth, guideline developers should pay attention to applicability.[25]

The quality assessment using AGREE II and RIGHT showed a certain consistency. There is some overlap between items of the two checklists, although they are classified and organized differently. AGREE II focuses more on guideline formation methodologies, while RIGHT pays more attention to reporting items. For example, AGREE II proposes requirements in search method, inclusion and exclusion criteria and updating procedure, while RIGHT contains more detailed items in basic information. From this perspective, different aspects and items of AGREE II and RIGHT can complement each other. A combination of the two checklists is recommended for guideline developers.[48]

Future perspectives for individualized therapy of antineoplastic drugs

Evidence accumulation. As evidence with the highest quality, guidelines are most frequently referred to in clinical practice. However, the development of more TDM guidelines for antineoplastic drugs is somewhat limited by inadequate evidence. Therefore, more evidence about the exposure–response relationship, PopPK, and dosing decision support is needed to facilitate the clinical implementation of TDM in oncology and optimize the use of antineoplastic drugs to improve patient outcomes.[49]

Nowadays, more studies are needed on the exposure–response relationship to support TDM-guided individualized administration of antineoplastic drugs. For example, with a narrow therapeutic range, 5-FU dosing by body surface area can only make a minority of patients achieve the desired therapeutic effect. By exploring the exposure–response relationship of 5-FU, the recommendation of a therapeutic exposure range of 20–30 mg×h/L was provided and applied, bringing significant benefits in efficacy and safety.[50,51] Moreover, the high drug acquisition costs of many antineoplastic drugs may make TDM-guided dosing cost-effective for patients and public health systems. More economic studies are still needed to evaluate the balance of the benefits and harms for recommendations in the short and long term.[20,52,47]

On the basis of a defined exposure–response relationship, it is suggested that PopPK models be developed to support dose individualization. Up to now, studies on PopPK have been conducted for a variety of antineoplastic drugs, including atezolizumab,[53] brentuximab vedotin,[54] busulfan,[9,11,55] dasatinib,[56] methotrexate,[7,57,58] sunitinib,[59] and vincristine[60,61] in pediatric patients and acalabrutinib,[62] afatinib,[63] atezolizumab,[53] brentuximab vedotin,[54] dostarlimab,[64] erlotinib,[65] necitumumab,[66] nivolumab,[67] pembrolizumab,[68] savolitinib plus osimertinib,[69] siltuximab,[70] and trastuzumab[71] in adults. Based on heterogeneous data, the quantification, and identification of variability and simulations, PopPK is an essential tool to individualize drug doses to reduce toxicity and improve patients' outcomes.[72]

Furthermore, researchers should develop tools that provide recommendations on the formulation and adjustment of drug therapy regimens. Combining PopPK models, individual patient factors and the measured drug concentration, Bayesian estimation can make a prediction of the complete concentration-time profile for patients.[73] Recently, model-informed precision dosing (MIPD), an approach to integrate TDM and PopPK, has gained increasing popularity, since it helps to maximize the success of PK/PD target attainment, and therefore maximize the efficacy and minimize the probability of toxicity.[74] Tools such as Autokinetics, BestDose, and NextDose for real-time MIPD of multiple drugs have been gradually applied in clinical practice.[75–77] In oncology, the development and application of these tools is limited and needs more attention.

Guideline implementation. In light of the findings in this study, TDM in oncology was unanimously recommended by current guidelines. When applying TDM guidelines in oncology, influencing factors should be taken into account, including technology levels, patient values, and costs.[1,78] Given the complexity of cancer treatment, TDM in oncology requires multidisciplinary teamwork.[79] Moreover, during the dissemination of TDM guidelines, all available resources need to be precisely identified and appropriately utilized.[80–82] Notably, the implementation status of TDM and compliance with relevant guidelines should be carefully evaluated to further promote standardized and rational implementation of TDM, ultimately improving treatment outcomes.

It is recommended that specific cases be provided when developing guidelines to illustrate the implementation of recommendations more effectively.

Take the implementation of CHINA-TDM 2022 as an example, a 42-year-old female patient exhibited methotrexate accumulation ($C_{24h\text{-}MTX}$ = 120.63 μmol/L) and a rapid increase in serum creatinine (Scr) levels (Scr = 275 μmol/L) on the second day following high-dose methotrexate therapy. Leveraging pharmaceutical expertize and the guideline, clinical pharmacists comprehensively assessed the patient's condition and assisted in devising the plan aimed at strengthening supportive care, including increasing leucovorin dose, strengthening personalized hydration, continuously alkalizing the urine to maintain the urine pH above 7.0, giving other symptomatic treatments (such as gargling for preventing oral mucositis), and close monitoring of blood concentrations and potential complications.[34] Eventually, through multidisciplinary collaboration and monitoring, the patient's blood methotrexate concentration was successfully brought down to a safe level, without any irreversible kidney damage or other serious adverse events.

Limitations

Our findings must be interpreted with caution considering limitations. First, we only included guidelines written in English or Chinese, which may cause some omissions. However, we searched international professional organizations and related reviews to mitigate the impact. Second, the recommendations of guidelines do not always reflect real-world clinical practice. In view of this, we combined clinical reality and the literature, including surveys and reviews, in our study. Additionally, we plan to conduct studies on the dissemination and implementation of these guidelines. Third, we calculated average scores or average reporting rates in each domain, whether for AGREE II or RIGHT, without considering differences in the importance of each domain and item. Thus, the comparison of scores or proportions should be interpreted with caution.

Conclusion

From the perspective of current guidelines, TDM approaches are now being expanded from cytotoxic antineoplastic drugs to newer targeted treatments. However, the types of antineoplastic drugs involved are still small, and there is still room for improvement in the quality of TDM guidelines for antineoplastic drugs. Furthermore, the reflected gaps warrant future studies into the exposure–response relationship and PopPK models. To further support the individualized therapy of antineoplastic drugs, the implementation of TDM in oncology can be improved through effective actions directed toward impact factors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Xinya Li: Data curation; Formal analysis; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

Zaiwei Song: Conceptualization; Formal analysis; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

Zhanmiao Yi: Methodology; Validation; Visualization; Writing – review & editing.

Jiguang Qin: Data curation; Writing – review & editing.

Dan Jiang: Data curation; Writing – review & editing.

Zhitong Wang: Data curation; Writing – review & editing.

Huibo Li: Validation; Writing – review & editing.

Rongsheng Zhao: Conceptualization; Funding acquisition; Project administration; Supervision; Writing – review & editing.

Acknowledgements

The abstract of this manuscript was accepted as oral presentation at the 21st International Congress of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT 2023).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (NSFC) (72074005, 72304007), the National Key R&D Program of China (2020YFC2008305), and the Beijing Health Science Technology Achievements and

Appropriate Technology Promotion Project (BHTPP2022079).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its Supplemental information files].

ORCID iDs

Xinya Li https://orcid.org/0000-0002-7539-8194

Zaiwei Song https://orcid.org/0000-0001-7064-4459

Zhanmiao Yi https://orcid.org/0000-0001-8575-3770

Rongsheng Zhao https://orcid.org/0000-0002-3266-3496

Supplemental material

Supplemental material for this article is available online.

References

1. Salman B and Al-Khabori M. Applications and challenges in therapeutic drug monitoring of cancer treatment: a review. *J Oncol Pharm Pract* 2021; 27: 693–701.
2. Nguyen NH, Solitano V, Vuyyuru SK, *et al.* Proactive therapeutic drug monitoring versus conventional management for inflammatory bowel diseases: a systematic review and meta-analysis. *Gastroenterology* 2022; 163: 937–949.e2.
3. Imani S, Alffenaar JW, Cotta MO, *et al.* Therapeutic drug monitoring of commonly used anti-infective agents: a nationwide cross-sectional survey of Australian hospital practices. *Int J Antimicrob Agents* 2020; 56: 106180.
4. Hiemke C, Bergemann N, Clement HW, *et al.* Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry* 2018; 51: 9–62.
5. Lo Re F, Angelini J, Sponga S, *et al.* Therapeutic drug monitoring of mycophenolic acid as a precision medicine tool for heart transplant patients: results of an Observational Pharmacokinetic Pilot Study. *Pharmaceutics* 2022; 14: 1304.
6. Noda S, Morita SY and Terada T. Dose individualization of oral multi-kinase inhibitors for the implementation of therapeutic drug monitoring. *Biol Pharm Bull* 2022; 45: 814–823.
7. Medellin-Garibay SE, Hernández-Villa N and Correa-González LC. Population pharmacokinetics of methotrexate in Mexican pediatric patients with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 2020; 85: 21–31.
8. Mueller-Schoell A, Groenland SL, Scherf-Clavel O, *et al.* Therapeutic drug monitoring of oral targeted antineoplastic drugs. *Eur J Clin Pharmacol* 2021; 77: 441–464.
9. Goutelle S, Thoma Y, Buffet R, *et al.* Implementation and cross-validation of a pharmacokinetic model for precision dosing of busulfan in hematopoietic stem cell transplanted children. *Pharmaceutics* 2022; 14: 2107.
10. Al-Metwali B and Mulla H. Personalised dosing of medicines for children. *J Pharm Pharmacol* 2017; 69: 514–524.
11. Bartelink IH, Lalmohamed A, van Reij EM, *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: e526–e536.
12. Wilkinson DS. Therapeutic drug monitoring in oncology. *Ther Drug Monit* 2019; 41: 551–552.
13. Han J, Sauberan J, Tran MT, *et al.* Implementation of Vancomycin Therapeutic Monitoring Guidelines: focus on Bayesian estimation tools in neonatal and pediatric patients. *Ther Drug Monit* 2022; 44: 241–252.
14. Matsumoto K, Oda K, Shoji K, *et al.* Clinical practice guidelines for therapeutic drug monitoring of vancomycin in the frame-work of model-informed precision dosing: a consensus review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. *Pharmaceutics* 2022; 14: 489.
15. Hamada Y, Tokimatsu I, Mikamo H, *et al.* Practice guidelines for therapeutic drug monitoring of voriconazole: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. *J Infect Chemother* 2013; 19: 381–392.
16. Wicha SG, Märtson AG, Nielsen EI, *et al.* From therapeutic drug monitoring to model-informed precision dosing for antibiotics. *Clin Pharmacol Ther* 2021; 109: 928–941.
17. de Jonge ME, Huitema AD, Schellens JH, *et al.* Individualised cancer chemotherapy:

strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review. *Clin Pharmacokinet* 2005; 44: 147–173.

18. Menz BD, Stocker SL, Verougstraete N, *et al.* Barriers and opportunities for the clinical implementation of therapeutic drug monitoring in oncology. *Br J Clin Pharmacol* 2021; 87: 227–236.
19. Annual report of national adverse drug reaction monitoring, https://www.nmpa.gov.cn/xxgk/fgwj/gzwj/gzwjyp/20220329161925106.html (2021, accessed 30 March 2023).
20. Vithanachchi DT, Maujean A, Downes MJ, *et al.* A comprehensive review of economic evaluations of therapeutic drug monitoring interventions for cancer treatments. *Br J Clin Pharmacol* 2021; 87: 271–283.
21. Shaneyfelt T. Pyramids are guides not rules: the evolution of the evidence pyramid. *Evid Based Med* 2016; 21: 121–122.
22. Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
23. Brouwers MC, Kho ME, Browman GP, *et al.* Development of the AGREE II, part 1: performance, usefulness and areas for improvement. *CMAJ* 2010; 182: 1045–1052.
24. Brouwers MC, Kho ME, Browman GP, *et al.* Development of the AGREE II, part 2: assessment of validity of items and tools to support application. *CMAJ* 2010; 182: E472–E478.
25. Chen Y, Yang K, Marušic A, *et al.* A reporting tool for practice guidelines in health care: the RIGHT Statement. *Ann Intern Med* 2017; 166: 128–132.
26. Campbell M, McKenzie JE, Sowden A, *et al.* Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020; 368: l6890.
27. Yu H, Steeghs N, Nijenhuis CM, *et al.* Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. *Clin Pharmacokinet* 2014; 53: 305–325.
28. NICE. Fluorouracil chemotherapy: the My5-FU assay for guiding dose adjustment, https://www.nice.org.uk/guidance/dg36 (2014, accessed 30 March 2023).
29. Verheijen RB, Yu H, Schellens JHM, *et al.* Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacol Ther* 2017; 102: 765–776.
30. Beumer JH, Chu E, Allegra C, *et al.* Therapeutic drug monitoring in oncology: international association of therapeutic drug monitoring and clinical toxicology recommendations for 5-fluorouracil therapy. *Clin Pharmacol Ther* 2019; 105: 598–613.
31. Hamzic S, Aebi S, Joerger M, *et al.* Fluoropyrimidine chemotherapy: recommendations for DPYD genotyping and therapeutic drug monitoring of the Swiss Group of Pharmacogenomics and Personalised Therapy. *Swiss Med Wkly* 2020; 150: w20375.
32. Chinese Pharmacological Society and China-Japan Friendship Hospital. Pharmacy expert consensus on the therapeutic drug monitoring of antitumor biosimilars (2020 edition). *Eval Analysis Drug-Use Hosp China* 2020; 20: 513–517+520.
33. Clarke WA, Chatelut E, Fotoohi AK, *et al.* Therapeutic drug monitoring in oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology consensus guidelines for imatinib therapy. *Eur J Cancer* 2021; 157: 428–440.
34. Song Z, Hu Y, Liu S, *et al.* Medication therapy of high-dose methotrexate: an evidence-based practice guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. *Br J Clin Pharmacol* 2022; 88: 2456–2472.
35. Smita P, Narayan PA, Kumaravel J, *et al.* Therapeutic drug monitoring for cytotoxic anticancer drugs: principles and evidence-based practices. *Front Oncol* 2022; 12: 1015200.
36. BTG Pharmaceuticals statement on NCCN clinical practice guidelines in oncology (NCCN Guidelines) recommendation for use of glucarpidase (Voraxaze) and MTXPK.org. BTG Pharmaceuticals, https://btgsp.com/en-us/about/news/btg-pharmaceuticals-statement-on-nccn-clinical-pra (2023, accessed June 28, 2023).
37. van der Kleij MBA, Guchelaar NAD, Mathijssen RHJ, *et al.* Therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacokinet* 2023; 62: 1333–1364.
38. Verougstraete N, Stove V, Verstraete AG, *et al.* Therapeutic drug monitoring of tyrosine kinase inhibitors using dried blood microsamples. *Front Oncol* 2022; 12: 821807.
39. Knezevic CE and Clarke W. Cancer chemotherapy: the case for therapeutic drug monitoring. *Ther Drug Monit* 2020; 42: 6–19.

40. George R, Haywood A, Khan S, *et al.* Enhancement and suppression of ionization in drug analysis using HPLC-MS/MS in Support of therapeutic drug monitoring: a review of current knowledge of its minimization and assessment. *Ther Drug Monit* 2018; 40: 1–8.
41. Zijp TR, Izzah Z, Åberg C, *et al.* Clinical value of emerging bioanalytical methods for drug measurements: a scoping review of their applicability for medication adherence and therapeutic drug monitoring. *Drugs* 2021; 81: 1983–2002.
42. Ye ZK, Li C and Zhai SD. Guidelines for therapeutic drug monitoring of vancomycin: a systematic review. *PLoS One* 2014; 9: e99044.
43. Zeng M, Yi Q, Zeng L, *et al.* Quality of therapeutic drug monitoring guidelines is suboptimal: an evaluation using the Appraisal of Guidelines for Research and Evaluation II instrument. *J Clin Epidemiol* 2020; 120: 47–58.
44. Wayant C, Cooper C, Turner D, *et al*. Evaluation of the NCCN guidelines using the RIGHT Statement and AGREE-II instrument: a cross-sectional review. *BMJ Evid Based Med* 2019; 24: 219–226.
45. Qaseem A, Forland F, Macbeth F, *et al.* Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012; 156: 525–531.
46. World Health Organization. *WHO handbook for guideline development*. 2nd ed. WHO Press, Geneva, 2014.
47. Lenzer J, Hoffman JR, Furberg CD, *et al.* Ensuring the integrity of clinical practice guidelines: a tool for protecting patients. *BMJ* 2013; 347: f5535.
48. Yao X, Ma J, Wang Q, *et al*. A comparison of AGREE and RIGHT: which Clinical Practice Guideline Reporting Checklist should be followed by guideline developers? *J Gen Intern Med* 2020; 35: 894–898.
49. Veal GJ, Amankwatia EB, Paludetto MN, *et al.* Pharmacodynamic therapeutic drug monitoring for cancer: challenges, advances, and future opportunities. *Ther Drug Monit* 2019; 41: 142–159.
50. Martin JH and Olver I. Precision medicine-based drug treatment individualization in oncology. *Br J Clin Pharmacol* 2021; 87: 223–226.
51. Schneider JJ, Galettis P and Martin JH. Overcoming barriers to implementing precision dosing with 5-fluorouracil and capecitabine. *Br J Clin Pharmacol* 2021; 87: 317–325.
52. Erku D, Schneider J and Scuffham P. A framework for economic evaluation of therapeutic drug monitoring-guided dosing in oncology. *Pharmacol Res Perspect* 2021; 9: e00862.
53. Shemesh CS, Chanu P, Jamsen K, *et al.* Population pharmacokinetics, exposure-safety, and immunogenicity of atezolizumab in pediatric and young adult patients with cancer. *J Immunother Cancer* 2019; 7: 314.
54. Suri A, Mould DR, Song G, *et al*. Population pharmacokinetics of brentuximab vedotin in adult and pediatric patients with relapsed/refractory hematologic malignancies: model-informed hypothesis generation for pediatric dosing regimens. *J Clin Pharmacol* 2020; 60: 1585–1597.
55. Alsultan A, Albassam AA, Alturki A, *et al*. Population pharmacokinetics of busulfan in Saudi pediatric patients undergoing hematopoietic stem cell transplantation. *Int J Clin Pharm* 2020; 42: 703–712.
56. Yang F, Zhang L, Zhao BB, *et al*. Population pharmacokinetics and safety of dasatinib in chinese children with core-binding factor acute myeloid leukemia. *Clin Pharmacokinet* 2022; 61: 71–81.
57. Beechinor RJ, Thompson PA, Hwang MF, *et al*. The population pharmacokinetics of high-dose methotrexate in infants with acute lymphoblastic leukemia highlight the need for bedside individualized dose adjustment: a report from the Children's Oncology Group. *Clin Pharmacokinet* 2019; 58: 899–910.
58. Panetta JC, Roberts JK, Huang J, *et al*. Pharmacokinetic basis for dosing high-dose methotrexate in infants and young children with malignant brain tumours. *Br J Clin Pharmacol* 2020; 86: 362–371.
59. Wang E, DuBois SG, Wetmore C, *et al*. Population pharmacokinetics-pharmacodynamics of sunitinib in pediatric patients with solid tumors. *Cancer Chemother Pharmacol* 2020; 86: 181–192.
60. van de Velde ME, Panetta JC, Wilhelm AJ, *et al*. Population pharmacokinetics of vincristine related to infusion duration and peripheral neuropathy in pediatric oncology patients. *Cancers (Basel)* 2020; 12: 1789.
61. Nijstad AL, Chu WY, de Vos-Kerkhof E, *et al*. A population pharmacokinetic modelling approach to unravel the complex pharmacokinetics of vincristine in children. *Pharm Res* 2022; 39: 2487–2495.
62. Edlund H, Bellanti F, Liu H, *et al*. Improved characterization of the pharmacokinetics of acalabrutinib and its pharmacologically active metabolite, ACP-5862, in patients with B-cell malignancies and in healthy subjects using a

population pharmacokinetic approach. *Br J Clin Pharmacol* 2022; 88: 846–852.

63. Freiwald M, Schmid U, Fleury A, *et al.* Population pharmacokinetics of afatinib, an irreversible ErbB family blocker, in patients with various solid tumors. *Cancer Chemother Pharmacol* 2014; 73: 759–770.
64. Melhem M, Hanze E, Lu S, *et al.* Population pharmacokinetics and exposure-response of anti-programmed cell death protein-1 monoclonal antibody dostarlimab in advanced solid tumours. *Br J Clin Pharmacol* 2022; 88: 4142–4154.
65. Fukudo M, Ikemi Y, Togashi Y, *et al.* Population pharmacokinetics/pharmacodynamics of erlotinib and pharmacogenomic analysis of plasma and cerebrospinal fluid drug concentrations in Japanese patients with non-small cell lung cancer. *Clin Pharmacokinet* 2013; 52: 593–609.
66. Long A, Chigutsa E and Wallin J. Population pharmacokinetics of necitumumab in cancer patients. *Clin Pharmacokinet* 2017; 56: 505–514.
67. Osawa M, Hasegawa M, Bello A, *et al.* Population pharmacokinetics analysis of nivolumab in Asian and non-Asian patients with gastric and gastro-esophageal junction cancers. *Cancer Chemother Pharmacol* 2019; 83: 705–715.
68. Freshwater T, Kondic A, Ahamadi M, *et al.* Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother Cancer* 2017; 5: 43.
69. Jones RDO, Petersson K, Tabatabai A, *et al.* Pharmacokinetic/pharmacodynamic analysis of savolitinib plus osimertinib in an EGFR mutation-positive, MET-amplified non-small cell lung cancer model. *Mol Cancer Ther* 2023; 22: 679–690.
70. Nikanjam M, Yang J and Capparelli EV. Population pharmacokinetics of siltuximab: impact of disease state. *Cancer Chemother Pharmacol* 2019; 84: 993–1001.
71. Chen X, Li C, Ewesuedo R, *et al.* Population pharmacokinetics of PF-05280014 (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer. *Cancer Chemother Pharmacol* 2019; 84: 83–92.
72. Sassen SDT, Zwaan CM, van der Sluis IM, *et al.* Pharmacokinetics and population pharmacokinetics in pediatric oncology. *Pediatr Blood Cancer* 2020; 67: e28132.
73. Del Valle-Moreno P, Ciudad-Gutiérrez P, Herrera-Hidalgo L, *et al.* Pharmacokinetic software for therapeutic drug monitoring: a scoping review protocol. *Farm Hosp* 2021; 45: 109–112.
74. Mena M, Garcia JC and Bustos RH. Implementing vancomycin population pharmacokinetic models: an app for individualized antibiotic therapy in critically ill patients. *Antibiotics (Basel)* 2023; 12: 301.
75. Roggeveen LF, Guo T, Fleuren LM, *et al.* Right dose, right now: bedside, real-time, data-driven, and personalised antibiotic dosing in critically ill patients with sepsis or septic shock – a two-centre randomised clinical trial. *Crit Care* 2022; 26: 265.
76. Heitzmann J, Thoma Y, Bricca R, *et al.* Implementation and comparison of two pharmacometric tools for model-based therapeutic drug monitoring and precision dosing of daptomycin. *Pharmaceutics* 2022; 14: 114.
77. Kantasiripitak W, Van Daele R, Gijsen M, *et al.* Software tools for model-informed precision dosing: how well do they satisfy the needs? *Front Pharmacol* 2020; 11: 620.
78. Wensing M, Wollersheim H and Grol R. Organizational interventions to implement improvements in patient care: a structured review of reviews. *Implement Sci* 2006; 1: 2.
79. Wang Y, Dai Y, Yang J, *et al.* A survey about the contents and features of oncology clinical pharmacy services and self-evaluations of the oncology pharmacists in China. *J Clin Pharm Ther* 2020; 45: 1106–1113.
80. Flottorp SA, Oxman AD, Krause J, *et al.* A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 2013; 8: 35.
81. Gagliardi AR. 'More bang for the buck': exploring optimal approaches for guideline implementation through interviews with international developers. *BMC Health Serv Res* 2012; 12: 404.
82. Shekelle P, Woolf S, Grimshaw JM, *et al.* Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development. *Implement Sci* 2012; 7: 62.