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Original Article

Optimizing Treatment, Minimizing Risk: Therapeutic Drug Monitoring in Hematological Malignancies

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Abstract. ***Background*****: The therapeutic landscape of hematological malignancies has expanded rapidly, increasing survival but also exposing patients to pharmacokinetic variability and clinically relevant drug–drug interactions. Therapeutic drug monitoring (TDM) offers a pharmacokinetics-informed strategy to individualize dosing, yet its real-world implementation across drug classes and healthcare settings remains insufficiently characterized.**
Methods**: We conducted an international, cross-sectional online survey (December 2023–February 2024) assessing availability, utilization, and clinical impact of TDM in patients with hematological malignancies. Physicians from multiple specialties reported institutional practices, turnaround times, drug-specific monitoring strategies, and treatment modifications based on TDM results.**
Results**: A total of 209 physicians from 32 countries participated, predominantly from Europe (92%). TDM was widely accessible (97%), mainly performed onsite (79%), and perceived as beneficial by nearly all respondents (99%). Routine TDM was most frequently used for classical agents (methotrexate, cyclosporin A), antifungals, and antibiotics, but substantial interest was reported for targeted therapies, including BCL-2 inhibitors, BCR-ABL tyrosine kinase inhibitors, FLT3 inhibitors, and Bruton tyrosine kinase inhibitors. Treatment was modified based on TDM results by 71% of respondents, with faster turnaround times strongly associated with clinical action. Limited assay availability, delayed reporting, and insufficient clinical evidence were identified as key barriers to broader implementation.**
Conclusions**: TDM is widely available and perceived as clinically useful in the management of hematological malignancies, frequently informing treatment decisions.While firmly established**

for classical agents and anti-infectives, clinicians express growing interest in extending TDM to targeted therapies. Optimizing turnaround times, expanding assay availability, and integrating pharmacokinetics-informed dosing into clinical trials may further clarify the role of TDM within precision medicine approaches in hematology.

Keywords: Therapeutic drug monitoring; hematology; Precision medicine; Drug–drug interactions; Targeted therapy; Antifungal; Dose adjustment; Clinical decision-making.

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Introduction. Over the past decades, the number of drugs available for patients with hematological malignancies has steadily increased, resulting in higher rates of long-term remissions and overall survival. However, the growing number of therapeutic agents has raised concerns about patient safety regarding the risk of over- or underexposure due to pharmacokinetic variability and drug–drug interactions when co-administered with other drugs.[1] Therapeutic drug monitoring (TDM) is an established pharmacokinetic tool aimed at supporting patient safety and therapeutic efficacy throughout the course of therapy. Measurement of plasma drug levels can detect potentially toxic or subtherapeutic concentrations of drugs that may lead to toxicity or treatment failure. TDM helps to monitor individual drug exposure over time and to support dose individualization based on pharmacokinetic evidence.[1] This is well recognized for several first-generation therapies used in hematology, including antimetabolites and other cytotoxic agents, which can induce severe toxicity in a concentration-dependent manner.[2] However, newer agents, including tyrosine kinase inhibitors (TKi), can also expose patients to adverse events related to pharmacokinetic variability, off-target toxicity, or clinically relevant drug–drug interactions (DDI).[3]

In the era of precision medicine, clinicians increasingly recognize the limitations of fixed-dose strategies, particularly with respect to toxicity and treatment failure due to over- or under-exposure, respectively. TDM can help to move from a fixed-dose paradigm toward individualized, pharmacokinetics-informed dosing strategies. TDM can enable early identification of deviations from therapeutic windows, thereby supporting clinical decision-making and optimizing treatment strategies.

To describe the current utilization of TDM in clinical practice, its accessibility, and its perceived role in treatment optimization and patient management, we coordinated an international survey among physicians treating patients with hematological malignancies.

Methods. The online questionnaire was carried out from December 2023 to February 2024. The electronic case report is accessible via https://www.clinicalsurveys.net/uc/HematoTDM/ (EFS, TIVIAN GmbH; Germany, Cologne). Responses were checked for accuracy, coherence, and completeness in order to guarantee the quality of the data. The survey covered the specializations of the participants – including hematology, infectious diseases, critical care, internal medicine, oncology, pediatrics, or pharmacy – with all questions explicitly referring to TDM practices in patients with hematological malignancies, institutional profiles such as patient numbers, availability of TDM, features of routine TDM (in-house versus outsourced), turnaround times, drug-specific TDM practices, and the effect of TDM on treatment adjustments. Participants were recruited through targeted email invitations distributed via professional networks and scientific societies. As the survey link was disseminated through multiple overlapping channels, the total number of invited physicians or centers could not be reliably quantified, precluding calculation of a response rate. Given the voluntary and self-reported nature of participation, the survey is subject to selection and response bias, particularly favoring clinicians with an interest or access to TDM.

Frequencies and percentages were used to analyze and compile the data that had been gathered. Proportion comparison was performed using Fisher's exact test or χ^2 test, as appropriate. All statistical analyses were conducted using SPSS v27.0 (SPSS, IBM Corp., Chicago, IL, United States).

Results. A total of 209 physicians from 32 countries participated in the survey, with the majority of

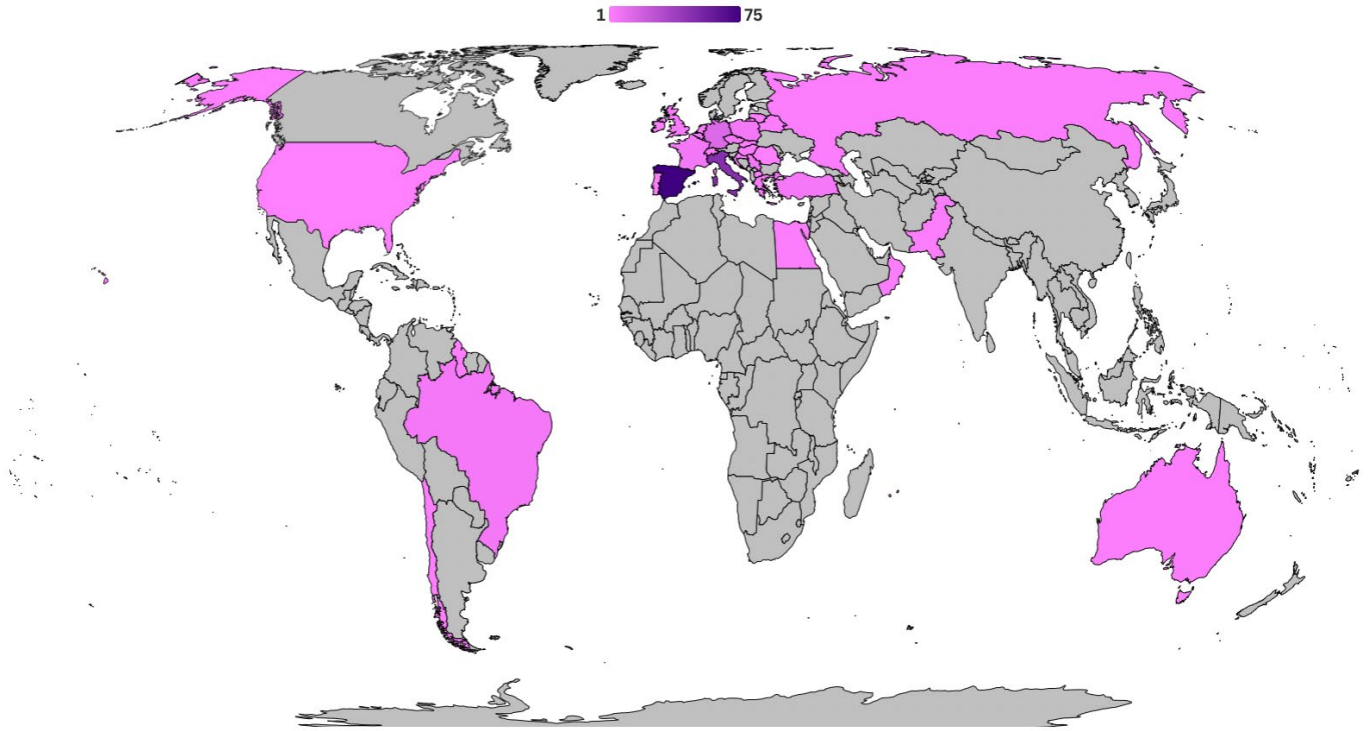

Figure 1. Global snapshot of participating centers, illustrating the predominance of European participation and the broad, though uneven, international distribution of respondents. Origin country of participants is: Spain (n=75, 35.9%); Italy (n=47, 22.5%); Germany (n=14, 6.7%); Belgium, Brazil, Czechia, France, Poland, Serbia, and Turkey (n=5, 2.4% each); United Kingdom (n=4, 1.9%); Greece and Hungary (n=3, 1.4% each); Australia, Belarus, Croatia, Egypt, Netherlands, Oman, Pakistan, Portugal, and Russia (n=2, 1.0% each); and Argentina, Chile, Guyana, Ireland, Lithuania, North Macedonia, Romania, Slovakia, Switzerland, and United States (n=1, 0.5% each).

respondents based in Europe (192/209, 92%) (**Figure 1**). Participants were predominantly from the fields of hematology (118/209, 57%), infectious diseases (42/209, 20%), internal medicine (36/209, 17%), and oncology (27/209, 12.9%). Most respondents were affiliated with large hospitals, with 138/209 (66%) reporting institutions with more than 500 beds, and teaching hospitals represented 101/209 (48.3%) of the cohort. Larger hospitals exhibited lower rates of outsourcing for TDM ($p<0.001$), a pattern particularly evident in centers performing chimeric antigen receptor T-cell (CAR-T) therapies ($p=0.020$) (**Table 1**, **Supplementary table 1**).

Therapeutic drug monitoring was widely available, with 202/209 (96.7%) participants reporting access to TDM, most commonly onsite (164/209, 78.5%). TDM was perceived as beneficial by 207/209 (99%) respondents. Turnaround times varied considerably, with 57/209 (27%) receiving results on the same day, 114/209 (55%) within 1–3 days, and 26/209 (12%) after more than 3 days. Longer turnaround times were more frequently observed for outsourced testing ($p<0.001$). Satisfaction with reporting times was positive in 111/209 (54%) of respondents, negative in 19/209 (9%), and occasionally dissatisfied in 70/209 (34%), with significantly lower satisfaction reported for outsourced TDM ($p<0.001$) (**Table 1**, **Supplementary table 1**).

Routine TDM was most commonly performed for classical agents, including cyclosporin A (168/209, 81%), methotrexate (170/209, 82%), and antifungal agents such as voriconazole (141/209, 68%) and posaconazole (91/209, 44%). Among antibiotics, vancomycin (175/209, 84%), amikacin (121/209, 58%), and gentamicin (98/209, 47%) were frequently monitored. Interest in TDM for newer targeted drugs was also notable, with routine monitoring reported for Bcl-2 inhibitors (99/209, 47%), Bcr-Abl TKi (94/209, 45%), FLT3 inhibitors (84/209, 40%), and BTKi (69/209, 33%) (**Table 1**, **Supplementary table 1**).

Among participants who did not routinely perform TDM, some reported requesting TDM selectively, including in cases of toxicity (59/209, 28%) and in regimens involving multiple drugs with potential drug-drug interactions (47/209, 22%). Therapy modifications based on TDM results were reported by 147/209 (71%) of participants, with an additional 54/209 (26%) adjusting therapy occasionally. Shorter turnaround times were associated with a higher likelihood of treatment modification ($p<0.001$). Factors influencing TDM utilization included situations in which clinical judgment outweighed TDM results (33/209, 16%), the need for repeat testing (16/209, 8%), and concerns that delayed TDM results no longer reflected the current clinical situation (29/209, 14%) (**Table 1**, **Supplementary table 1**).

Discussion. In this international survey including 209 physicians from 32 countries, we found that TDM is widely available (97%), most frequently onsite, and considered beneficial in almost all cases (99%). Importantly, these findings reflect clinicians' perceived

Table 1. Participant characteristics, institutional profiles, and therapeutic drug monitoring practices in hematology care.

	Overall	
	n	%
Participant specialty		
Hematology	118	56.5
Oncology	27	12.9
Pediatrics	11	5.3
Intensive care	5	2.4
Internal medicine	36	17.2
Pharmacy	4	1.9
Infectious diseases	42	20.1
Other	7	3.3
Institution profile		
General/Acute care hospital	58	27.8
Regional/County hospital	11	5.3
Specialized hospital	29	13.9
Teaching hospital	101	48.3
Outpatient clinic	0	0.0
Other	10	4.8
Institution size		
<200 beds	20	9.6
200-500 beds	51	24.4
>500 beds	138	66.0
Hematology beds		
0-20 beds	61	29.2
21-50 beds	98	46.9
>51 beds	50	23.9
Hospital target		
Adult	108	51.7
Children	7	3.3
Both	94	45.0
Hematological targets		
Acute leukemia	198	94.7
Chronic leukemia	197	94.3
Lymphoma/Multiple myeloma	206	98.6
Autologous HSCT	183	87.6
Allogeneic HSCT	149	71.3
CAR-T	112	53.6
Annual hematological inpatients		
<200 hospitalizations	30	14.4
201-500 hospitalizations	78	37.3
>501 hospitalizations	101	48.3
TDM found to be beneficial	207	99.0
TDM availability	202	96.7
Onsite	164	78.5
Outsourced	36	17.2
TDM turnaround time		
Same day	57	27.3
1-3 days	114	54.5

	Overall	
	n	%
>3 days	26	12.4
Turnaround satisfaction		
Yes	111	53.1
No	19	9.1
Not always	70	33.5
Routine TDM		
Antineoplastics		
Busulfan	28	13.4
Cyclosporin A	168	80.4
Methotrexate	170	81.3
Antifungals		
Isavuconazole	59	28.2
Itraconazole	33	15.8
Posaconazole	91	43.5
Voriconazole	141	67.5
Flucytosine	8	3.8
Antibiotics		
Amikacin	121	57.9
Fluoroquinolones	14	6.7
Gentamicin	98	46.9
Linezolid	46	22.0
Vancomycin	175	83.7
TDM-based therapy adjustment		
No	1	0.5
Yes	147	70.3
Sometimes	54	25.8
Clinical evidence can outweigh TDM in decisions	33	15.8
Second TDM sometimes needed	16	7.7
Delayed TDM may be outdated	29	13.9
Routine TDM for…		
Yes		
BTKi	69	33.0
Bcl-2i	99	47.4
Bcr-Abl TKi	94	45.0
FLT3i	84	40.2
IDH1/2i	49	23.4
No, but would consider		
If toxicity	59	28.2
To assure monitoring levels/response	57	27.3
If suspected interactions	47	22.5
No, generally not	17	8.1
Interest related to TDM…		
Clinical		
BTKi	75	35.9
Bcl-2i	95	45.5
Bcr-Abl TKi	80	38.3
FLT3i	78	37.3

	Overall	
	n	%
IDH1/2i	49	23.4
Research		
BTKi	53	25.4
Bcl-2i	69	33.0
Bcr-Abl TKi	49	23.4
FLT3i	62	29.7
IDH1/2i	42	20.1

Comparison per TDM availability, TDM performance, TDM turnaround time, and TDM-based modification are provided in the **Supplementary table 1**.

Bcl-2i, B-cell lymphoma 2 inhibitor; Bcr-Abl TKi, breakpoint cluster region–Abelson tyrosine kinase inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor t-cell therapy; FLT3i, FMS-like tyrosine kinase 3 inhibitor; HSCT, hematopoietic stem cell transplantation; IDH1/2i, isocitrate dehydrogenase 1/2 inhibitor; p value, probability value (statistical significance); TDM, therapeutic drug monitoring.

clinical utility of TDM and its influence on decision-making, rather than demonstrated improvements in patient outcomes. Turnaround times strongly influenced satisfaction, with shorter times correlating with higher likelihood of treatment modifications. Routine use was most frequent for classical agents such as methotrexate and cyclosporin A, as well as for antifungals and antibiotics, but a growing interest was reported in extending TDM to targeted therapies including Bcl-2 inhibitors, Bcr-Abl inhibitors, and BTKi. Importantly, more than two-thirds of respondents reported adapting treatment based on TDM results, underscoring its perceived clinical relevance in routine practice.

Regardless of geographic area, our survey demonstrates broad access to TDM for different drug classes, including chemotherapy, targeted agents, antibiotics, and triazole antifungals. However, the predominance of European respondents (92%) limits the generalizability of these findings to other regions, particularly low- and middle-income countries (LMICs) and North American healthcare systems. Access to laboratory infrastructure, validated assays, turnaround times, and reimbursement models may differ substantially across income settings, potentially limiting feasibility of routine TDM implementation outside high-resource European centers. TDM was perceived as beneficial by most participants, especially by those who had access to TDM on-site with more rapid turnaround times. Moreover, our survey revealed substantial clinician interest in extending TDM to targeted drugs for which routine monitoring is not yet widely available, such as BTKi and Bcl-2 inhibitors.

The broad use of TDM among participants supports its role within a multidisciplinary approach to the management of patients with hematological malignancies.[1] However, implementation of TDM for targeted therapies—particularly TKIs—remains heterogeneous. For many targeted agents, validated therapeutic ranges are lacking, exposure–response relationships are incompletely defined, and TDM is not routinely endorsed by regulatory authorities. Current barriers include limited assay availability, lack of standardization across laboratories, inter-assay variability, and insufficient prospective outcome data. Thus, while clinician interest is substantial, TDM for targeted therapies remains largely exploratory and should be interpreted cautiously until supported by outcome-driven evidence. Despite their designed selectivity, these drugs can inhibit multiple kinases, resulting in off-target toxicity.[1,4] TDM is generally recommended when a robust exposure–response and/or exposure–toxicity relationship has been established. For some targeted agents, emerging evidence supports TDM and proposed target ranges, although high-quality outcome data remain limited.[3] From a feasibility standpoint, TDM is most readily implemented for drugs with well-characterized pharmacokinetics, commercially available assays, and predictable pharmacodynamic effects. Drugs with narrow therapeutic windows, high inter-patient variability, or those metabolized by polymorphic enzymes are particularly suitable for routine monitoring. For certain drug classes, particularly antifungal azoles, prospective and quasi-prospective studies have demonstrated associations between TDM-guided dosing and improved efficacy or reduced toxicity, supporting its integration into routine care. In contrast, outcome-driven evidence for TDM of kinase inhibitors remains limited.[3,5-7]

Furthermore, many TKI are substrate of cytochrome P450 (*CYP450*) and, therefore, when co-administered with *CYP450* inhibitors DDI may occur, resulting in plasma overexposure and increased risk of toxicity of the respective targeted drug,[1,8,9] and TDM may help identify and mitigate such pharmacokinetic alterations in selected clinical scenarios. For antifungal agents, especially triazoles, prospective and quasi-prospective studies have linked TDM-guided dosing to improved efficacy and reduced toxicity, supporting its routine use. In contrast,

such outcome-linked evidence remains limited for most kinase inhibitors. These effects may be mitigated by optimizing doses through utilization of TDM.[5,10] A specific situation are DDI with antifungals in a prophylactic setting where patients at high risk of invasive fungal diseases receive triazole prophylaxis such as posaconazole.[11-13] Posaconazole is a strong *CYP3A4* inhibitor thereby reducing the metabolism of many drugs, including TKi and BTKi, resulting in plasma overexposure and increased risk of toxicity.[1,14] Regarding application, TDM is not limited to trough (Cmin) or peak (Cmax) measurements. While antifungal azoles are typically monitored at trough to ensure adequate exposure, peak measurements may be relevant not only for certain cytotoxic agents but also for aminoglycosides to avoid acute toxicity. Alternative approaches, such as limited sampling strategies and area-under-the-curve (AUC)–based monitoring, may further enhance individualized dosing, depending on the pharmacological properties of the drug. Tailoring the sampling strategy to the pharmacokinetics of the individual drug is crucial to maximize the clinical utility of TDM.

Through incorporation of TDM into clinical routine, treatment of hematological diseases may move toward target concentration–driven dosing strategies, potentially influencing clinical trial design and regulatory frameworks. However, economic constraints, logistical challenges, assay availability, turnaround times, insufficient clinical evidence for certain drugs, and limited expertise in interpretation may hamper broader implementation. Personalized TDM-guided dosing may improve outcomes and quality of life through minimization of toxicity, although prospective studies are needed to confirm its impact on clinical endpoints.[15] Beyond clinical considerations, pharmacoeconomic implications are increasingly relevant. By preventing severe toxicity, avoiding ineffective dosing, and potentially reducing hospitalizations or treatment interruptions, TDM may contribute to more cost-effective care. Nevertheless, formal cost-effectiveness analyses in hematological malignancies are scarce and warrant further investigation.

This study has several limitations. First, the majority of responses were obtained from large tertiary-care centers (>500 beds), which may not accurately reflect practices in smaller or peripheral hospitals. Second, the predominance of European respondents (92%) limits the generalizability of these findings to other regions, particularly low- and middle-income countries (LMICs) and North American healthcare systems. Access to TDM infrastructure, availability of validated assays, laboratory turnaround times, and reimbursement structures may differ substantially across income settings and healthcare models, potentially leading to lower feasibility of routine TDM implementation outside high-resource European centers. Country-level participation was uneven, and the survey was not powered to allow robust national comparisons, limiting inferences at the country or healthcare-system level. Third, the survey relied on self-reported practices, which may be subject to recall or reporting bias. Fourth, the survey design inherently carries a risk of selection and response bias, as physicians with a particular interest in therapeutic drug monitoring may have been more likely to participate. Consequently, the findings may overestimate both availability and perceived utility of TDM compared with unselected hematology care settings. Finally, due to the cross-sectional design, we could not assess longitudinal changes in TDM utilization or its direct impact on patient outcomes.

Conclusions. TDM is widely available and perceived as clinically useful in the care of patients with hematological malignancies, frequently informing therapeutic decisions. While its role is well established for classical agents and anti-infectives, extension to targeted therapies requires further validation. Future efforts should focus on improving turnaround times, expanding assay availability, and incorporating pharmacokinetics-guided dosing into prospective clinical trials to define its role within precision medicine in hematology.

Contributors. All authors contributed to study design and study supervision. JSG did the statistical analysis. PM, JS, and JSG interpreted the data and wrote the paper. All the authors recruited, and documented participants, critically read, reviewed, and agreed to publish the manuscript.

Data sharing statement. The corresponding author can provide the data supporting the findings of this study upon a reasonable request. All authors had full access to the data and had final responsibility for the decision to submit for publication.

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