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ORIGINAL RESEARCH

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A Delphi study to determine the epidemiology and clinical management of patients treated with HDMTX who develop methotrexate (MTX) delayed elimination in France, Germany, Italy, and the UK

Stefan Bielack[1] | Christopher P. Fox[2] | Khê Hoang-Xuan[3] | Ariadna Giró-Perafita[4] | Carmelo Rizzari[5,6]

[1]Cooperative Osteosarcoma Study Group, Pediatric Oncology, Hematology, Immunology, Klinikum Stuttgart-Olgahospital, Stuttgart Cancer Center, Stuttgart, Germany

[2]School of Medicine, University of Nottingham, Nottingham, UK

[3]IHU, Department of Neuro-oncology Mazarin, APHP, Sorbonne University, Paris, France

[4]Omakase Consulting S.L., Barcelona, Spain

[5]Unit of Pediatrics, University of Milano-Bicocca, Monza, Italy

[6]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

Correspondence
Carmelo Rizzari, Unit of Pediatrics, University of Milano-Bicocca, Monza, Italy.
Email: carmelo.rizzari@gmail.com

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Abstract

Introduction: High-dose methotrexate (HDMTX) is administered for the treatment of some malignancies. Serious complications after the administration of HDMTX are rare, but occasionally MTX may precipitate in the renal tubes causing a delayed elimination leading to renal, multiorgan toxicities and to life-threatening complications. This study aims to estimate the incidence and clinical management of delayed MTX elimination in France, Germany, Italy, and the UK.

Methods: Twelve haemato-oncology and pediatric oncology clinical experts from leading European hospitals participated in the study. A two-round Delphi methodology was used to gather data on different variables relevant to evaluate the HDMTX induced-toxicity impact. For quantitative data, median and interquartile ranges were calculated. Data on prevalence was calculated considering the number of patients in each hospital and the population they cover, and then, extrapolated to the country population.

Results: The total number of patients treated annually with HDMTX in France, Germany, Italy, and the UK is estimated in 7155. Of these, 16% are estimated to develop delayed MTX elimination and around 9% may develop HDMTX-induced acute kidney injury (AKI). Leucovorin, hyperhydration and urine alkalinization are applied to prevent MTX toxicity and precipitation whilst glucarpidase, hemofiltration and hemodialysis are being used for persisting toxic MTX serum levels. Grade 3 systemic toxicities are common in these patients, hematologic and gastrointestinal being the most common ones.

Conclusions: This report provides expert clinical practice experience and opinion of the incidence and management of HDMTX-delayed elimination in France, Germany, Italy and the UK, thereby contributing to the evidence available on this relevant medical condition which can be life-threatening.

KEYWORDS
acute kidney injury (AKI), epidemiology, high-dose methotrexate (HDMTX), methotrexate delayed elimination, MTX toxicity clinical management

1 | INTRODUCTION

Methotrexate (MTX) is considered an essential component of therapy for many cancers such as non-Hodgkin lymphoma, acute lymphoblastic leukemia (ALL) and osteosarcoma.[1–6] High-dose MTX (HDMTX), defined as a drug-dose higher than 500 mg/m^2, requires careful supportive measures to enhance the solubility of MTX and its metabolites in urine to prevent the potentially lethal MTX toxicity.[7,8] Although HDMTX can thus be safely administered to most patients, it can precipitate in the renal tubes causing severe toxicity. Renal toxicity leads to impaired MTX clearance and prolonged drug exposure at toxic concentrations, which further worsen renal function and exacerbate non-renal adverse events, including myelosuppression, mucositis, neurotoxicity, dermatologic and gastrointestinal toxicity, and hepatotoxicity.[8–11] Acute kidney injury (AKI) and other toxicities can lead to significant morbidity and oncologic treatment delays.[12] Serum creatinine, urine pH and output, and serum MTX concentration are usually monitored to assess renal clearance with concurrent supportive care measures to prevent renal and other systemic toxicity.[12]

The incidence of delayed MTX elimination has been explored in several studies.[13–22] The percentage of patients that may develop this condition may vary depending on the underlying disease, treatment, and age ranging from 9% to 15% in osteosarcoma to 31.9% in non-Hodgkin lymphoma.[12–17,22] Importantly, since the development of some these studies, protocols have been updated and new alternatives for treating this condition have become available.

This study aims to determine the epidemiology, clinical and therapeutic management and the unmet needs of patients receiving HDMTX, as part of their chemotherapy treatment, who develop methotrexate toxicity due to delayed methotrexate elimination in the real clinical practice in Europe, to reflect the current management of these patients. The study was developed in collaboration with experts directly involved in the daily management of these patients from France (FR), Germany (GR), Italy (IT) and the UK.

2 | METHODS

2.1 | Design of the study

The Delphi methodology is a structured process that uses interactions with experts via questionnaires to reach consensus on complex issues, preserving the anonymity of the participants.[23,24] In this study, a two-round Delphi methodology was followed.

2.2 | Panel selection

The selection of the clinical experts invited to participate in the study was based on the following criteria: (1) Experience in haemato-oncology and/or pediatric oncology, specifically in leukemia, lymphoma and osteosarcoma. (2) Experience with HDMTX treatment in their respective countries. (3) Relevant publications of scientific articles, guidelines, and conference proceedings regarding HDMTX and/or MTX toxicity. (4) Willingness to participate in the study.

2.3 | Questionnaire development

The questionnaire used in this Delphi study is an adaptation of the questionnaire developed in a previous study to determine the epidemiology and management of delayed MTX elimination in Spain.[25] The adapted questionnaire is composed of a set of 56 open-ended and close-ended items. The first section explored the epidemiology of HDMTX treated patients who then develop delayed MTX elimination. The second part focused on the clinical and therapeutic management of these patients and included: clinical guidelines and protocols, supportive care measures, patient monitoring, identification and treatment, outocmes and limitations of current treatments, and unmet needs.

2.4 | Methodology of Delphi study

The clinical experts who participated in this study responded to the two Delphi rounds between July 2021 and January 2022. In the first round, the questionnaire was sent to the clinical experts through the SurveyMonkey platform. In the second Delphi round, the consensus and validation of the information obtained in the first round was sought via a questionnaire presented in a Microsoft Word document.

2.5 | Data analysis

Microsoft Office Excel was used for the statistical analysis of the Delphi data.

All quantitative answers are expressed as median (Q1–Q3). Descriptive analysis was performed for the patient management and clinical variables. For multiple-choice questions, each response option was analyzed individually to determine the percentage of clinical experts that selected it. When necessary, the median class of the answers was calculated. Any qualitative comment was analyzed to complement the information obtained. Consensus was considered when at least 80% of

the experts agreed on a topic.[26] The second-round questionnaire was designed based on the analysis of the data obtained in the first round and focused on obtaining consensus on the questions where there was a greater dispersion of responses during the first round.

The number of patients treated with HDMTX annually was estimated by calculating the annual prevalence for each hospital. This calculation involved considering the patients reported by the experts and adjusting for the hospital's coverage. The prevalence was then expressed as the number of patients per 100,000 inhabitants. Subsequently, the median prevalence derived from this analysis was extrapolated to the total population of each country using the latest data available from national statistics bodies (Figure S1).

To estimate the annual incidence of specific conditions related to HDMTX treatment, the percentage of patients reported by the experts was utilized. The following conditions were included: (i) delayed MTX clearance, (ii) HDMTX-induced AKI, (iii) severe systemic toxicities, and (iv) deaths due to delayed MTX elimination.

3 | RESULTS

3.1 | Expert panel

Twelve clinical experts from France ($n = 2$), Germany ($n = 2$), Italy ($n = 3$) and the UK ($n = 5$) were recruited to participate in the study and all of them completed the questionnaires of both Delphi rounds. Main characteristics of the experts are presented in Table 1.

TABLE 1 Expert panel characteristics.

Expert's characteristics	%	$n = 12$
Countries		
France	17%	2
Germany	17%	2
Italy	25%	3
UK	42%	5
Years of experience		
11-20 years	42%	5
More than 20 years	58%	7
Specialties		
Acute Lymphoblastic Leukemia (ALL)	43%	6
Lymphoma	43%	6
Osteosarcoma	14%	2
Pediatric hematology-oncology	7%	1
Type of Patient Treated		
Adult	33%	4
Pediatric (<18 years)	58%	7
Both	8%	1

[a]Includes both adult and pediatric.

3.2 | Epidemiology of HDMTX-induced AKI due to delayed MTX elimination in France, Germany, Italy, and the UK

The estimated number of patients (i) treated with HDMTX, (ii) patients presenting delayed MTX elimination, (iii) HDMTX-induced AKI, (iv) severe systemic toxicities by country are shown in in Table 2. According to the experts' answers, approximately 7155 patients would receive HDMTX annually in the countries included in the study (estimated incidence 2.60 [1.74–4.00]/100,000 inhabitants). Out of these 7155 patients treated with HDMTX, 1146 patients (16.0%) are estimated to develop a delay in MTX clearance and approximately 650 patients (9.1%) would develop HDMTX-induced AKI. Amongst patients with HDMTX-induced AKI, 276 (42.5%) each year are estimated to develop severe extra-renal/systemic toxicities.

The percentage of adult patients treated with HDMTX presenting with delayed MTX elimination is higher than in pediatric patients according to the experts' answers, estimated at 20.0% versus 13.6% respectively (Table 3). Adult patients were estimated to have a higher probability to developed HDMTX-induced AKI than pediatric patients, estimated in 11.8% and 7.5% of patients treated with HDMTX, respectively. The development of severe extra-renal/systemic toxicities in patients developing HDMTX-induced AKI is more common in adult patients than pediatric patients, representing 53.9% and 31.7% respectively.

TABLE 2 Estimated number of patients with HDMTX administration, delayed MTX elimination, HDMTX-induced AKI and its clinical consequences by country.

	France	Germany	Italy	UK	Total
Patients treated with HDMTX	1706	2164	1540	1745	**7155**
Delayed MTX elimination	273	347	247	279	**1146**
HDMTX-induced AKI	155	197	140	158	**650**
Developing severe extra-renal/systemic toxicities (≥grade 3)	66	84	59	67	**276**

In line with previous observations, the mortality was estimated to be much higher in adult than in pediatric patients, with death rates of almost 3% in adult patients compared to less than 0.5% in pediatric patients.

3.3 | Clinical and therapeutic management of patients receiving HDMTX in France, Germany, Italy, and the UK

3.3.1 | Clinical guidelines

Experts reported that 83% of hospitals included in the study had a specific protocol for the management of MTX toxicity due to delayed

elimination. Nevertheless, most of the clinical experts also referred to national and international guidelines for the management of delayed MTX elimination which vary according to the country (Table 4)

3.3.2 | MTX serum level monitoring and detection of delayed MTX elimination

All the clinical experts used MTX serum concentration measurements as the main method to monitor for possible MTX-induced toxicity after HDMTX-infusion, and 75% of them reported using the immuno-enzymatic assay (fluorescence polarization immunoassay, FPI). Three of the experts did not know or could not answer to this question. One hospital in France uses the HPLC (High Performance Liquid Chromatography) technique but only after the administration of glucarpidase to better follow the MTX serum levels decay.

Most of the clinical experts routinely perform creatinine levels assessment (100%), urinary flow (92%) and urine pH (92%) measurements, as well as assessment of bilirubin levels (83%). Furthermore, 67% of the experts perform assessments of GOT (glutamate-oxaloacetate transaminase) and GPT (glutamate-pyruvate transaminase). All clinical experts use leucovorin, fluid hydration and urine alkalinization as supportive care measures to prevent HDMTX-induced toxicity.

TABLE 3 Estimated percentage (%) of patients with delayed MTX elimination, HDMTX-induced AKI and its clinical consequences by type of population.

	Total*	Adult	Pediatric
Patients treated with HDMTX with HDMTX that develop delayed MTX elimination	16.0%	20.0%	13.6%
Patients treated with HDMTX that develop HDMTX-induces AKI	9.1%	11.8%	7.5%
Patients with HDMTX-induces AKI developing severe extra-renal/ systemic toxicities (≥grade 3)	42.5%	53.9%	31.7%
Mortality (due to delayed MTX elimination)	0.83%	2.9%	< 0.5%

Abbreviations: AKI, acute kidney injury; HDMTX, high dose of methotrexate; MT, methotrexate.

3.3.3 | HDMTX-induced toxicity management

All experts agreed that increased creatinine levels and elevated MTX serum levels are the most relevant parameters to identify a possible HDMTX-induced AKI within the first 24–48 h after any HDMTX infusion. Other parameters considered are low urinary flow, low urine pH, and other MTX-toxicity related symptomatology.

The experts agreed than once a delayed MTX elimination is detected, patients are usually treated with high leucovorin doses to avoid MTX toxicity plus increased supportive care measures (urine alkalinization and fluid hydration) to increase MTX solubilization. In case MTX levels do not decrease and toxicity persists, different treatments are available in expert's hospitals (Table 5). The most common treatment used in case of delayed MTX elimination or HDMTX-induced AKI were glucarpidase (23% and 41% of the patients received, respectively), followed by haemofiltration (4% and 6% of the patients received, respectively) (Table 5).

TABLE 4 National and international guidelines for the management of HDMTX-induced toxicity mentioned by the interviewed experts.

Guide	Percentage of experts (*n* = 12)	France (*n* = 2)	Germany (*n* = 2)	Italy (*n* = 3)	UK (*n* = 5)
NHS England Clinical Commissioning Policy: Glucarpidase for the urgent treatment of methotrexate-induced renal dysfunction[27]	33% (4)				4
ANSM Voraxaze ATU guideline[28]	25% (3)	2		1[a]	
Ramsey L. et al. Consensus guideline for the use of glucarpidase in patients with HDMTX induced AKI and delayed methotrexate clearance (2018). Oncologist[7]	17% (2)			2	
AIEOP-BFM ALL 2017 Protocol[29]	17% (2)		1	1[a]	
UpToDate website Therapeutic use and toxicity of high-dose methotrexate[30]	8% (1)			1[a]	
Advice in individual disease specific cancer treatment protocol.	8% (1)				1
Recommendations from the "Réseau Expert National pour les Lymphomes Oculo-Cérébraux"	8% (1)	1[a]			
None	8% (1)		1		

Abreviations: NHS, National Health System; ANSM, Agence Nationale de Sécurité du Médicament et des produits de santé; ALEOP-BFM ALL, Treatment Protocol for Children and Adolescents with Acute Lymphoblastic Leukemia.

[a]One of the participants may refer to more than one clinical guideline.

TABLE 5 Treatment availability in hospitals included in the study and median percentage of patients receiving each of the treatments.

	Hospitals with availability	Patients with delayed MTX elimination receiving the treatment	Patients with HDMTX-induced AKI receiving the treatment
Treatment	%	%	%
Glucarpidase	91%	23%	41%
Hemofiltration	82%	4%	6%
Hemodialysis	82%	3%	5%
Exchange transfusion/plasma exchange	55%	0%	0%
Peritoneal dialysis	45%	0%	0%
High-flux dialysis	27%	0%	0%

Abbreviations: HDMTX, high dose of methotrexate; MTX, methotrexate.

TABLE 6 Estimated incidence of grade 3 non-renal systemic toxicities in patients with HDMTX-induced AKI.

		Percentage of patients presenting grade 3 toxicity						
Type of toxicity	Experts reporting the toxicity (n)	≤ 10%	11%–20%	21%–40%	41%–60%	61%–80%	>80%	Median class
Hematologic	11	1	3	4	2	-	1	21-40%
Gastrointestinal	10	3	1	4	1	-	1	21-40%
Hepatic	11	3	4	1	1	2	-	11-20%
Myelotoxicity	10	1	4	1	3	-	1	11-20%
Mucositis	11	2	4	1	2	-	2	11-20%
Infections	10	4	3	1	1	1	-	11-20%
Neurologic	8	6	2	-	-	-	-	≤10%
Pulmonary	3	3	-	-	-	-	-	≤10%

Interestingly, 92% of the clinical experts reported that they usually use glucarpidase when patients develop a significant deterioration in renal function after the start of HDMTX, defined by toxic plasma MTX levels and increasing serum creatinine levels compared to baseline.

Regarding extracorporeal methods used for the treatment of HDMTX-induced toxicity, 83% of the clinical experts agreed that extracorporeal methods are resources considered intensive and invasive for the patients, and 67% considered that they showed only limited and slow effect to reduce plasma MTX concentrations. Furthermore, 42% of them also considered that those methods are associated with high rates of MTX rebound with increased toxicity and morbidity.

Instead, 100% of the experts, when asked about the benefits of glucarpidase compared to extracorporeal methods, agreed that glucarpidase is more effective in reducing MTX levels, as well as quicker to administer and easier to manage. Almost all experts (83%) considered that glucarpidase is less invasive and reduces the frequency or severity of systemic non-renal toxicity versus extracorporeal treatments. Moreover, experts reported that fewer patients treated with glucarpidase developed MTX rebound associated toxicity (6% [1–28]) compared to extracorporeal methods (40% [11–68]).

However, the experts also highlighted some considerations on the use of glucarpidase, which included its cost, the limited stock of the drug in numerous hospitals as well the slow process to gain access to it.

Regarding the clinicians involved in the management and treatment of patients with delayed MTX elimination, 75% of experts indicated that nephrologists are usually involved, as well as other specialists such as hospital pharmacists, clinical pharmacology laboratories, endocrinologists, and, for pediatric patients, PICU (Pediatric Intensive Care Unit) experts, especially when a dialytic procedure is needed in pediatric patients.

3.3.4 | HDMTX-induced secondary systemic toxicities

Grade 3 non-renal systemic toxicities were reported to be common in patients with delayed MTX elimination, hematologic and gastrointestinal toxicity being the most common events (observed in 21%–40% of patients), followed by hepatic toxicity, infections, myelotoxicity, and mucositis (observed in 11%–20% of patients) (Table 6).

Patients presenting with delayed MTX elimination and inadequate response to increased supportive care measures have a median length of hospital stay (LOS) of 8 [7–10] days. The estimated percentage of patients that required admission to the Intensive Care Unit (ICU) ranged from 0% to 50% (median 0% [0–14,9]), depending on the type of patient treated (adult/pediatric) and disease.

3.3.5 | Unmet needs

The most relevant unmet needs for patients with delayed MTX elimination considered by the clinical experts were the need for early intervention for affected patients (75%), a quicker access to glucarpidase (67%) and a clear evidence-based national guidelines on when to intervene with rescue therapy (58%). Notwithstanding, 92% of clinicians agreed that if glucarpidase was not available at their hospital, there would be a clear unmet need for patients with delayed MTX elimination, as more patients would present with severe toxicities and require intensive care. In addition, all experts agreed that using glucarpidase earlier in time (according to plasma MTX levels and creatinine levels) would reduce the morbidity in these patients, with 92% and 83% of the experts agreeing that it would also reduce the severity of AKI and therefore reduce the length of hospital stay, respectively.

The clinical experts were also asked about aspects to improve the care of patients with delayed MTX elimination. Most relevant topics, considered by 75% of the experts, were the availability of a safe, effective, and rapid rescue treatment to clear MTX and avoid further complications, the development of specific national guidelines for the management of HDMTX-induced toxicity, the availability of a fast and effective treatment, and a specific training on MTX monitoring and rescue treatments. Other needs were also considered a priority for some of the experts, such as the improvement of methods to manage MTX toxicity and prevent toxicities (58%), improvement of MTX monitoring methods (42%), and a better access to emergency medicine (42%).

4 | DISCUSSION

HDMTX-induced AKI due to delayed MTX clearance is a rare and life-threatening condition that leads to severe complications and long-term consequences, such as severe systemic toxicities or even death. In addition, these complications can involve a delay or suspension of antineoplastic treatment which could translate into increased morbidity and mortality.

To elucidate current epidemiology and clinical management of delayed MTX elimination in France, Germany, Italy and the UK, a Delphi study was conducted with 12 experts directly involved in the daily management of these patients.

The total number of patients treated with HDMTX annually in these countries is estimated at 7155. Of these, 16% are expected to develop delayed MTX elimination and about 9% would develop HDMTX-induced AKI, of which almost half of them are expected to develop severe extra-renal/systemic renal toxicities. The most common complications the experts observed were hematologic toxicities, gastrointestinal toxicity, hepatotoxicity, mucositis, and myelotoxicity. The incidences of these short- and long-term consequences are in agreement with previous studies, showing that gastrointestinal toxicity, mucositis, and hepatotoxicity were the most common.[11,19] The mortality was estimated at almost 1% of the whole population, being higher in adults than pediatric populations (2.9% vs. <0.5%).

Across the four European countries, it is estimated that nearly 300 patients develop severe (≥grade 3) extra-renal/systemic toxicities each year. It is important that physicians are aware of these potential toxicities and take prompt and effective action when they occur. Primary treatment are the measures directed at countering delayed MTX elimination and returning MTX to below toxic levels. Supportive measures may include antiemetics, dexamethasone and further hydration for patients with vomiting or nausea, ice chips for the relief of mucositis, and corticosteroids (or cyclophosphamide in advanced cases) for patients with pulmonary toxicity.[31]

The percentage of patients with HDMTX-induced toxicity obtained are in line with previous studies.[12–17,22] For instance, the study conducted by *Bacci G*. et al. showed that 8.6% of osteosarcoma patients treated with HDMTX showed delayed MTX elimination.[13] The retrospective studies of *May J*. et al. and *Ranchon F*. et al., which included mostly patients with lymphoma, showed higher rates of MTX delayed elimination in these patients with an incidence of 31.9% of HDMTX cycles and 35.2% of the patients, respectively.[14,15] Regarding the HDMTX-induced renal toxicity, ranged from 1.8%[22] in osteosarcoma patients and 10.6% in patient with lymphoma.[15] Likewise, delayed clearance of MTX was significantly higher in adult patients (over 20) than in younger patients (16% vs. 6%).[13]

The results of this Delphi Study are also similar to those recently published in a survey of experts from Spain.[25] For instance, the proportion of HDMTX-treated patients with MTX elimination delay in this study was estimated in 16%, while was almost 28% according to the results of the Spanish Delphi Study.[25] In line, the percentage of patients developing HDMTX-induced AKI in this study was estimated at 9% versus the 12% in the Spanish study.[25] The differences observed in the estimated percentages could be explained by the different availability of glucarpidase in the respective hospitals included in both studies, which varied from 91% in FR, GR, IT, UK to 60% in Spain. This would also potentially impact in the estimated mortality of the former patients, which as lower (0.83%) in this study than in the Spanish Delphi study (4%),[25] being this last in line with previously reported studies where mortality rate ranged from 3% to 6%.[7,19,20,22]

Elevated MTX serum levels and increased serum creatinine levels are considered the most relevant parameters to identify HDMTX-induced AKI. Usually, patients with delayed MTX clearance are treated with increased leucovorin dosages and increased supportive care, in agreement with clinical guidelines and the literature.[17,20]

The clinical experts with previous experience in the use of glucarpidase noted that they assumed it to be more effective at reducing MTX levels, quicker to administer, easier to manage and less invasive compared with extracorporeal methods still considered slow

and to have a limited efficacy. Accordingly, all experts agreed that using glucarpidase earlier than it is currently commonly used would probably reduce the risks of toxicity, morbidity and mortality as well as reducing the severity of AKI and reducing the length of hospital stays. Although no direct comparison has been made between glucarpidase and extra-corporeal methods, a retrospective study with patients treated with glucarpidase or dialysis between 2010 and 2017 showed that mean length of hospital stay was 14.7 days for glucarpidase versus 40.2 days for dialysis group.[32] There is also a higher inpatient mortality in the dialysis group versus the glucarpidase group, with a mortality rate of 50.6% versus 3.3% respectively.[32]

Additionally, the development of national guidelines for HDMTX-induced toxicity, accurate training on HDMTX monitoring and associated rescue treatments as well as the availability of a safe, effective, and rapid rescue treatments to clear MTX and avoid further complications were highlighted as priority needs in this study.[12,33,34]

Some limitations of our study should be acknowledged. For instance, the sample size of the expert participating in the study ($n = 12$), which may result in limited representation of different clinical expertize and reduced statistical power. Nevertheless, a sample of about 10–30 participants has been overall suggested as being appropriate for a Delphi Study.[23,35,36] Furthermore, it is important to acknowledge that the distribution of experts across different countries in the study is uneven, which could introduce bias toward countries with greater representation. However, it is worth noting that the findings from sections 3.3.2 and 3.3.3 demonstrate that the management of these patients remains consistent across the participating countries, indicating that any potential bias related to representation does not significantly impact the results. The number of patients treated with HDMTX and its management has been estimated using data provided by clinical experts from leading hospitals of four different countries and may not represent the clinical practice of smaller hospitals. Finally, glucarpidase was not available in the hospital of one expert, and so their responses with regards glucarpidase are based primarily on published literature and discussion with colleagues, rather than direct practical clinical experience. Further studies based on real world data should be conducted to gain a deeper knowledge of the epidemiology and clinical burden of delayed MTX elimination.

5 | CONCLUSION

To the best of the authors' knowledge, this report represents the first exploration of the current epidemiology and clinical management of HDMTX-delayed elimination in main European countries. Drawing on expert opinion and informed by direct clinical experience for most authors and topics covered, it provides a comprehensive overview of the consequences associated with delayed MTX elimination. Despite its comparatively low incidence, delayed MTX elimination is considered to cause serious short- and long-term consequences for the patients. According to the experts questioned, the availability of safe, effective, and rapid treatments would help in these patients in reducing the incidence of associated severe toxicities.

AUTHOR CONTRIBUTIONS

Stefan Bielack: Formal analysis; Methodology; Validation; Writing—review & editing. **Christopher P Fox**: Formal analysis; Methodology; Validation; Writing—review & editing. **Khê Hoang-Xuan**: Formal analysis; Methodology; Validation; Writing—review & editing. **Ariadna Giró-Perafita**: Conceptualization; Formal analysis; Methodology; Writing—original draft. **Carmelo Rizzari**: Conceptualization; Formal analysis; Methodology; Validation; Writing—review & editing.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICTS OF INTEREST STATEMENT

SB, CPF and KH-X received consulting fees from BTG. AG-P is employee of Omakase Consulting S.L. Omakase Consulting S.L. received funding from SERB. CR has received fees from SERB Pharmaceuticals for consultation activities and participation in Advisory Boards.

TRANSPARENCY STATEMENT

The lead author Carmelo Rizzari affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Carmelo Rizzari http://orcid.org/0000-0002-4828-3893

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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