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Evidence Level For Therapeutic Drug Monitoring of Anticancer Drug : A Review of The Literature

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Abstract

Anticancer drugs have a narrow therapeutic index, high toxicity and they exhibit great interindividual pharmacocinetic variability. All these proofs make the therapeutic pharmacological monitoring necessary to improve the response and better control the toxicity of these agents which is studied by several studies contrary to the effectiveness of which the bibliographical data are limited.

The majority of randomized trials show that the most relevant pharmacokinetic parameter for these anticancer drugs is the area under the curve (AUC). Unfortunately until now TDM is still limited in daily practice for the majority of agents as the scarcity of published data from pharmacological trials, the use of these agents in combined protocols in different types of cancer and also the variety administration schedules. This reviewed article discusses common applications of anticancer drugs in evaluating the use of TDM by presenting their level of evidence. Some anticancer drugs commonly use TDM « major challenge » such as 5-Fu, methotrexate high dose, carboplatin whose dose adjustment is feasible and the dosage is based on pharmacokinetics which improved the therapeuticresponses in patients receivingthese drug by reduceing toxicity and increase efficacy.

Keywords: Anticancer Drug, Therapeutic Drug Monitoring, Pharmacokinetic, Toxicity, Efficacy, Level of Evidence

Introduction

Cancer drugs are systemic treatments that work on cancer cells regardless of their location throughout the body. They are characterized by significant toxicity resulting from their non-specific action on all rapidly multiplying cells. Most of these drugs are characterized by a strong dose-response relationship, the efficacy of which for these anticancer drugs is practically inseparable from their toxicity, and the therapeutic index of these drugs is very narrow. Interindividual pharmacokinetic variability is generally significant [1-4]. These data are a strong argument in favor of Therapeutic Drug Monitoring (TDM) which would allow the dose to be adjusted according to theindividual pharmacokinetic characteristics.TDM can be defined as the measurement of specific drugs and /or their metabolites concentrations in biological sample of treated patient such as plasma at timed intervals to allow better individual adaptation dosage of the treatment. This approach ensure the optimal concentration exposure in order to improve therapeutic efficacy and reduce toxicity. Several drugs that are controlled have a narrow « therapeutic index », which is defined as a ratio of the toxic dose to the effective dose of the drug. The choice of the drug which enters into this approach is based on the most important criterion which is the therapeutic index must be narrow. Not all drugs require therapeutic monitoring because most of these medication have a broad therapeutic index and are prescribed on the basis of preestablished dosage protocol such as hypertenseur drugs [5,6].
In practice, the majority of long-term treatments deserve to be piloted and monitoring their concentration can helpguarantee the effectiveness of these agents while minimizing their toxcitity. Generally, optimization of treatment (Dose) require an adequate and obvious biomarker which pharmacokinetic.

In oncology, TDM is an emerging disciplina. We know that the evidence for the effectiveness of anti-cancer drugs is scare and difficut to obtain, given the variation in protocols and treatment modalities. The TDM of these agents is based on their respective specificities characteristics: a narrow therapeutic range of concentration between toxicity and efficacy and their higer interindividual variability. Even, if there is no consensus for TDM, the practices are adaptable and have the capacity to evolve. Prospective clinical trials should help validate the benefit of dose individualization based on limited population and blood sampling procedures. When the clinical benefit of TDM for an agent has been demonstrated, it is mandatory that the greatest number of patients can benefit from it. This transition is a continuous process which regularly requires a synthesis of the results of research and the clinical disciplines concerned. Although this dose adjustment strategy allows for a usual management modality and TDM can only be noticed if it is practically feasible. However, there are limits which slows down the implementation of an TDM for certain anticancer drugs, these limits are of an analytical nature such as the dosing device used and organizational or methodological such as routine use of combination chemotherapies for many types of tumors, the paucity of published data from pharmacological trials, administration schedules and the difficulties of dose adaptation “in real time”For the different protocols used [7-10].The plasma concentrations of these agents are measured using mainly HPLC (High Performance Liquid Chromatography) with UV detection or fluorescence or HPLC coupled to mass spectrometry .

In this situation the question which arises: what is the level of evidence of TDM with respect to the arguments available in the literature? according to the methodology described by Guellec et al [11]. Different proofs must be determined such as: arguments in favor of the exposure-efficacity / toxicity relationship, clinical situations leading to changes in pharmacokinetic parameters; the biological parameters which can evaluate the clinical effect of the drug, the controlled concentration studied ... Indeed, the level of TDM evidence is determined following an evaluation of bibliographic data (Table1)

Table 1: The levels of evidence for therapeutic pharmacological monitoring according to the definition of the TDM group of the French Society of Pharmacology and Therapeutics

Level of recommendation	Arguments of the level recommendation
Essential	Clinical care directly depends on TDM TDM is mentioned in governmental drug approval
Strongly recommended	Randomized trials show that TDM is associated with improvement in terms of efficacy or toxicity Pharmacoeconomic studies show interest of TDM
Recommended	Nonrandomized trials show that TDM is associated with improvement in terms of efficacy or toxicity
Potentially useful	Drug is associated with pharmacokinetic variability and relationships between exposure and efficacy or toxicity are observed
Needed to be assessed	Drug is associated with pharmacokinetic variability but relationships between exposure and efficacy or toxicity are lackingTherapeutic range is often large

The aim of the present article is to evaluate the usefulness of TDM in somes anti cancer drugs and to discusses their current applications and also justify their level of evidence

Current Applications of Tdm in Anticancer Drug

Imatinib

Reasons of intervariability in Pk of imatinib

Imatinib is a tyrosine kinase inhibitor, used as a curative agent in the treatment of chronic myeloid leukemia (CML) [12-14], during the maintenance phase, and in the gastro-intestinal stromal tumor (GIST) [15]. In both indications, this drug is administered daily, at a dose varying between 400 and 600 mg in depending on cancer type and stade, it has been demonstrated that this dose was associated in some patient to a lack of response in cases of CML and/or GIST [16,4]. Moreover, standard prescribed doses of imatinib were associated with a large variations of trough concentrations [Cmin], ranging from 150 to 3910 ng/mL [17]. The inter-individual variability in C0 is estimated at 54.1% and 43.6%, respectively, in patients receiving 400mg and 600 mg daily [4,18].

The inter-individual variability of Imatinib concentration is mainly explained by many factors such as age, gender and body weight [2,17]. Moreover, the variabiltity in drug concentration is partly explained by polymorphisms in enzymes implicated in the metabolism of this chemotherapy agent. Indeed, Imatinib is metabolized by hepatic cytochrom CYP 450, mainly throughout its CYP 3A4 isoform [19]. The activity of CYP3A4 depends on drug-drug and drug – food interactions and environmental factor. This anticancer drug is eliminated predominantly via the bile; renal excretion plays a negligible role in imatinib elimination with a terminal elimination half time at 19.3 ± 4.4 hours [21] For all these reasons, TDM of this drug is mandatory to better assess the efficacy and toxicity of this agent.

Relationship drug concentration and efficacy

Several studies focused on pharmacokinetic/ pharmacodynamic relationship of Imatinib have demonstrated a positive correlation between trough concentrations (C0) of this drug and clinical response. The C0 threshold varied according to the type of tumor and/or the duration of treatment [2,8,21-22].
According to European LeukemiaNet (ELN) recommendations, an optimal clinical response in CML is defined as a BCR-ABL 1 transcript level ≤10% at 3 months; i.e, a complete cytogenetic response (CCyR) at 6 months, and ≤0.1%, i.e, a major molecular response(MMR) at 12 months or later [23].

Ishikawa et al in 2010 has found that a threshold C0 value of 974ng/ml was associated with a major molecular response (MMR) [24]. In two other studies, plasma imatinib concentration more than 1002 ng/ml and more than 1009 ng/ml were significantly associated with the achievement of satisfactory of both cytogenetic and molecular responses; respectively at 3 months and12 months and later (Awidi et al., 2010; Picard et al., 2007) [18,25]. Hence, it is suggested that patients reaching a plasma trough concentrations above 1000 ng/ml were more likely to achieve a satisfactory clinical response of CCR and MMR than

those having a concentration less than 1000 ng/ml [26,27].

For GIST, studies focusing on association between imatinib concentration and clinical outcomes are rare. In this respect, it has been demonstrated in a clinical trial that patients with Cmin at 1 month above 1110 ng/ml has better clinical outcome than those having a Cmin < 1110 ng/ml. Indeed, the response rate was at 67% and 74%, respectively, in patients having a Cmin < 1110 ng/ml and Cmin > 1110 ng/ml, (p=0.002) and the median time of tumor progression was at 11.3 and 30 months (p =0.003), respectively [26].

In another study, Bouchet et al have demonstrated that a threshold of 760 ng/ml Cmin of imatinib, performed at least 1 month of treatment, was associated with 65% reduction risk of progression (p: 0.0271) independently of the anatomical localization [28]. However, further studies are required to be defined a clear threshold in GIST patients.

Relationship drug concentration andtoxicity

Correlation between imatinib plasma concentration and toxicity is still controversial. Only limited studies have demonstrated a positive correlation between drug exposure and toxicity in CML patients. Delbaldo et al, showed that unbound drug exposure, i.e, the area under the curve was correlated to the hematological toxicity of imatinib [29,30]. In another study, Guilhotet al., have demonstrated that higher imatinib Cmin, greater than 3180 ng/mL, on Day 29 was associated with the frequency of all-grade neutropenia, anemia, and leukopenia and thrombocytopenia within the first three months of therapy [31].

Level Evidence Supporting imatinibTDM

However, 19 studies including a large sample size (4563 patients) weredone to further validate a Cmin therapeutic range of imatinib between 1000 to 1500 ng / mL because of a value > 1500 ng / mL would have increased the probability of toxicity.

Recently, asystematic review including 38 studies confirmed this recommended therapeutic range for this anticancer agent (1000 to 1500ng/ml). The authors concluded that TDM of imatinib is highly useful and "strongly recommended"to improve efficacy outcomes in patients with chronic phase CML treated with imatinib

Fluoro-uracile (5-FU)

5-FU is a pyrimidine analogue, which interfere with RNA and DNA synthesis constituents to prevent cell proliferation. Since its development over 50 years, this antineoplastic drug has improved response rates and survival in different type of cancer [32]. It is widely used in adjuvant, neoadjuvant and metastatic treatment of a range of cancer such as breast; esophageal, colorectal cancer [33,34]. Its combination with oxaliplatin, irinotecan and biological agent has shown a better efficacy than a monotherapy protocol [35,36].

Interindividual variability of 5-FU

Despite these improvements, resistance and toxicities to 5-FU remains a limitation to its therapeutic optimization. Indeed, different schedules of 5-FU administration, based on body surface area (BSA) or body weight [37], have been used, such as continuous i.v. infusion and bolus injection. However, these administration strategies leaded to a variability between patients in clinical response and occurrence of toxic side effetcs. This variability has been explained by a wide interindividual variability of 5-FU pharmacokinetics and has been demonstrated in several studies [38,39]. The correlation between 5-FU clerance and BSA has been proved in 81 patients with cancer colorectal metastatic who received a dose of 1.3mg/m^{2}continuous injection of 5-FU while 8h /j. They observed an important interindividual variability (10 fold) in plasma clairance from 0.49 to 4.93 L/h/m^2. Knowing that, BSA does not symbolise for may factor who are involved for a range of 5-FU such as genotype, age, gender, disease state, drug-drug interactions [40]. Similary pharmacokinetic study (in 13 gastrointestinal cancer patients) showed the 5-FU plasma clairance varied from 0.39 to 2.55 L/h/m^2 if the injection is by bolus at a dose of 15 mg / kg [41]. Whatever the infusion schedule, the clearance pharmacokinetic analysis revealed a significant interindividual variability. A small part of this variability has been attributed to demographic parameters (age, gender, weight) [42]. The variability of the activity of enzymes implicated in 5-FU metabolism has also been reported to have an impact on 5-FU pharmacokinetic.

Evaluation of 5-FU exposure-toxicity relationship

T2he relationships between pharmacokinetics/toxicity have been well explored in depth compared to the pharmacokinetic / efficacy relationship. Since the significant interindividual variability of 5-FU was observed whatever the mode of administration (bolus or continuous). Most studies treat the pharmacokinetics / toxicity relationships, in colorectal cancer patients with doses ranging from 370 and 600 mg / m2, have shown that the most common serious side effects are nausea (9.4% continuous infusion, 23% in bolus), diarrhea (about 13%), mucite (14.3% in bolus ; 26% continuous infusion) and 53% neutropenia [43,44]. Blaschke et al in 2013 have showed a good correlation between the concentration of 5-FU and the toxic effect of grade 3 and 4 [45]. The main cause of toxicity is known: it is a total or partial deficiency of DPD (dihydropyrimidine dehydrogenase) responsible for inactivating 5-FU. This enzyme is coded by DPYD gene and the 5-FU clerance is predominantly dependent on DPD. This letter plays an important role in catabolism of 5-FU which transforms 5-FU into inactive dihydro-5FU. 90% of the dose is degraded by DPD. The inter-individual variability observed in the DPD enzymatic activity is largely explained by a genetic factor who has been identified as a risk factor of fatal toxicities in deficient patients [46]. In addition, this deficit was observed with a severe risk or fatal excess toxicities in capecitabine (5-FU prodrug). Indeed, in the patient receiving a standard dose of 5-FU, any significant decrease in DPD activity will train an over dose which may cause an hematological and degistive toxicities [47]. This deficit, incaucasian population, can be complet (0.1% to 0.5% in population) or partiel (3% to 10% of patients). According to bibliographic data and recommendation, it is necessary to should be performed a DPD deficiency screening before initiating 5-FU treatement, especially in patient at high risk of toxicity or in an adjuvant situation [47,48].The search for DPD complete deficit will also lead to the identification of patients with a partial deficiency of this enzyme which occurs on the one hand by determining the mutations in the DPYD gene and on the other hand by phenotyping evaluation.From analytical point of view, this phenotype analysis and TDM of 5-FU is carried out by chromatographic technic. Itis determined by measurement of uracilemia (Overall marker enzyme activity) and calculation of the ratio dihydrouracil/uracil (UH2/U). An uracelemia value greater than 150 ng / ml suggests a complete DPD deficiency associated with a risk of severe toxicity from 5-FU. This correlation has been proven by several studies [46,51]. These toxicities are frequently observed during the first two cycles of chemotherapy leading to an increase in the concentration of 5-FU.

In patients with partial DPD deficiency, a reduced dose of 5-FU was used in the first cycle which will be followed by an adjustment of the 5-FU dose. This letter is based on pharmacokinetic data to avoid severe toxicities. Data bibliographic report a significant correlation between the ratio (UH2/U) /or uracelimia and the main pharmacokinetic parameters (clearance, plasma concentration). The relationship between drug exposure and response is well established when assessment is done at the concentration level and at the target site. Whether this relationship can provide a clarification for clinical result such as toxicity and / or efficacy. It is important to assess this relationship before initiating a 5-FU dose modification [49]. 5-FU is characterized by a narrow therapeutic index and a strong exposure-toxicity relationship. These conditions support the use of 5-FU TDM treatment method to optimize therapy and treatment in the future. Several studies have shown the interest of TDM for injectable forms during a randomized trial (fixed standard dose versus individually adapted dose), the results showed that in the group having benefited from a dose adaptation, the observed exposure was reduced, also the toxicity was less while the efficacy in both groups was similar [48,50]. Indeed, the toxicity incidence was significantly correlated with AUC [51-53]. The continuous infusion appears to be less toxic than the intravenous bolus. In the case of a continuous 5-day infusion, the therapeutic index of 5-FU is narrow, the AUC value is between 29 and 30 mg in patients with ORL cancer and who have a 5-day infusion. In the case of 8 hoursinfusions given to patients with metastasized colorectal cancer, severe toxicity was related to plasma concentrations greater than 3000 ng / mL (i.e. AUC0 → 8 h = 24 mg h / L). The AUC threshold value used for toxicity is 30 mg h / L in both ORL cancer and metastatic colorectal cancer(Picard et al., 2007). An initial dose of 1.5g/m2 5-FUwasinjectedin 104 patients with metastatic colorectal cancer (mCRC) (Table 2). Patients were randomized in two groups, one of this groups received a fixed dose throughout the cycle (without TDM) and another group received an initial dose of 5-FU and after all subsequent doses are adjusted weekly and guided by the result of pharmacokinetic (with TDM). Indeed, the dose of 5-FU subsequently administered in the following cycles was based on measurement of steady-state concentration (Css). The results showed that plasma concentration reached 2500 ng/mL to 3000 ng/ml, which corresponds to $AUC_{0\text{-}8}$20–24 mgh/L. The target concentration has been reached during 4 cycle in 94% of patients (with TDM) of which after 3 months, the dose mean administred in this group is 1790 mg/m2/week. Unlike the other group (without TDM) and with received a dose of 1.5 g/m2 5-FU. The result showed that plasma 5-FU levels were in the target therapeutic range in only 4

of 49 patients, on the other hand the plasma concentration found in 5 patients is in the toxic range and a discontinuation of treatment in one patient [48].

Table 2: Evidence level of TDM for platinum compounds and 5-FU as a function of cancer type

Deseases	**Doses**	**Regimen**	**Modalities of administration**	**Pharmaco kinetics (PK)**	**Lower limit of efficacy**	**Upper limit of efficacy**	**Pharmacodynamics relationships**	**Level of evidence for TDM**	**References**
Platinium salt									
Cisplatin in adult									
ovarian or testicular carcinoma	80-100mg/m^2	cisplatin	Continous infusion over 120h	Cmax	1.95µg/ml	-	Nephrotoxicity	Limited Recommendation	(Salas *et al;2006)*
Carboplatin in adult									
ovarian carcinoma of epithelial origin	40-1000 mg/m^2	carboplatin	120 h with dose adjustment		5	7	Thrombocytopenia, Ieukopenia	potentially useful	(Jodrell *et al ;1992)*
small cell lung carcinoma.			at 24 h	AUC	*mg.min/mL*	*mg.min/mL*			
Oxaliplatin in adult									
mCRC	85 -130 mg/m^2	oxaliplatin	2 -6 h	Clerance < 30 mL / min	-	-	Nephrotoxicity	potentially useful	(Gori *et al ;2014)*
Cancer colon				Dose reduced from 30% to 50%			Hematopoetic toxicity		
5- Fluouracil									
	1.5				20	24	**Leukopenia,** thrombocytopenia		
mCRC	g/m^2	5- FU		AUC_{0-8h}	mg/min/ml	mg/min/ml	**Toxicity:**mucositis, **diarrhea,-leukopenia,anemia**		(Lee et al ; 2016
			8h	Cmin	2500ng/ml	3000ng/ml		Strongly recommended	

CRC	1.3 g/m^2	5-FU +Leucovorin	8h	AUC_{0-8h} Cmin	16 mg/min/ml	24 mg/min/ml			(Gamelin *et al ;1999)*
					2000ng/ml	3000ng/ml			
Head and Neck	1g/m^2	5-FU+ oxaliplatin (130mg/m^2)+ folonic acid	Over 46h		20	30			(Goirand *et al ;2018)*
				$AUC_{0-5days}$	mg/min/ml	mg/min/ml			

The same team studied the effect of adjusting 5-FU dose according to the plasma concentration but the 5-FU (initial dose: 1.3g/ m2) is injected weekly with an association of 400mg/m2 locovorinin 152 patients with CRC. Ajustement of the 5-FU dose made every week according to the plasma concentration to reach the optima therapeutic range of 2000 to 3000 ng/ml correspond to AUC_{0-8h} 16-24 mgh/L (Table 2). After 3 months of treatment, 5-FU dose was increased in 124 patients, maintained in 6 patients and decreased 14 patients who have a plasmatic concentration greater than 3000 ng/ml which prompts the clinician to reduce immediatly the dose to avoid the acute toxicities such as diarrhea (39%) and hand-foot syndrome (30%). Therefore, the 3000 ng/ml of 5-FU plasmatic concentration were significant assocciated with a toxicity ($p < 0.0001$) [37]. Faty and al gave an infusion of 5-FUcombinedwithcisplatin to 106 patients, who have head and neck cancer, of whom 49 patients had TDM by the determination of AUC. The latter had a reduction in the dose during the second and third course of chemotherapy with an absence of mucositis (side effect). while the rest of the patients (57patients) are treated without TDM which causes significant neutropenia and thrombocytopenia compared to the group treated with TDM of the order of 17.5% vs 7.6% respectively [52].

Like wise a $AUC_{0-3days}$ was determined in 170 patients with squamous cell carcinoma of the head and neck receiving a course of chemotherapy of oxaliplatin associated with a continuous 5-day infusion of 5-FU. AUC analysis (AUC_{0-5day} = 20–30 mgh/L) led to adecision to reduce the 5-FU dose in 40% of patients (Table 2). This reduction generates a statistically significant improvement in response rates (effectiveness) of around 47% in the second chemotherapy cure compared to the chemotherapy-cure, which is around 31%. They also observed a reduction in the incidence of toxicity above grade 2 which is in the order of 12.4% in the second cure Vs 20% in the first cure [54].

All randomized controlled clinical trials have evaluated a potential decrease in toxicity in patients with 5-FU TDM. This significant reduction in 5-fu related diarrhea, hand-foot syndrome [55], mucositis and neutropenia, thrombocytopenia. Also, it is consistently documented in non-randomized clinical trials.

Evaluation of 5-FU exposure-efficacy relationship

The bibliographic data concerning the concentration-efficacy relationships are less thorough which is due to the diversity of the protocols and the use of associations with one or more cytotoxic agents, which does not allow obtaining clear data. Although some authors have tried to demonstrate these relationships such us the study of Gamelin et al 1996, was carried out on 40 patients in which those classified as responders had a higher 5-FU concentration than that of non-responders [56]. In addition, overall survival at one year was better in patients with a 5-FU concentration above the mean concentration (70.6%) compared to patients with a concentration below the mean concentration average (46%) [57]. However, this study was not powerful enough to examine the effect of 5-FU TDM on survival. As monotherapy, the randomized trial using a usual 5-FU (1500mg / m2) regimen showed that 5-FU TDM significantly improved overall response rates from 18% to 33% [58].

The antitumor activity of 5-FU (efficacy) is explained by its mechanism of action. When 5-FU was administered alone will generate a response rate of 10 to 15% and total survival about 10 months, which is an improvement in supportive care, which provided a survival of about six months. Thanks to the many protocols, 5-FU was not gived alone but it given combined with folinic acid or carboplatin. This combination improves the

response rate compared to using 5-FU alone, but provides little gain in total survival. All authors agree that the use of TDM improves clinical efficacy which is determined by response rate, not the survival rate, and reduction in overall toxicity [48].

In addition, whatever the diagram used in the administration of 5-fluorouracil (5-FU) alone or in combination regimens. The PK / PD relationship as observed for a single drug may differ from the exposure-effect relationship for a combination of drugs. Although, the combination therapy complicates the evaluation of therapeutic outcome and toxicity but the benefits of 5-FU TDM have been demonstrated for several cancer treatment protocols. Several studies have shown that a PK-based approach can effectively lead to improved clinical efficacy, therefore alleviates underdosing or overexposure to this drug, and reduced toxicity [53,56].

Level recommendation of 5-FU

In sammury, according to literature, there is sufficient evidence to stronglyrecommend TDM for the management of 5-FU therapy in patients with early or advanced CRC and patients with SCCHN receiving common 5-FU dosing regimens. The 5-fu obeys the criteria that justify the TDM (larger inter-individual variability than intra-individual variability, a narrow therapeutic index, established exposure-toxicity and activity relationships). The results of randomized trials have shown that TDM reduces the toxicity rates (primary endpoint) and variability in 5-FU exposure, while data on clinical benefit of 5-FU TDM is very limited despite improved response rates by this strategy, who attributes a reserved utility in efficiency but no survival benefit [54].

Methotrexate High doses

Methotrexate (MTX) is an antineoplastic drug, an analogue of folic acid. In high doses (MTX-HD), it is indicated in various solid cancers and malignant hemopathies, such as lymphoblastic leukemia (LAL), malignant lymphoma, osteosarcoma and non-Hodgkin lymphoma [59].

MTX nonspecifically inhibits dihydrofolate reductase (DHFR) and thymidylate synthetase (TS). This inhibition prevents the reduction of dihydrofolic acid to tetrahydrofolic acid and disrupts the synthesis of purine bases (adenin and guanin) and a pyrimidine base, thymidine, which are constituents of cellular DNA and RNA. Also MTX inhibits directly certain enzymes involved in the de novo synthesis of purines [60]. MTX – HD has a potential for serious toxicity [61]. This administration is always done with sequential administration of folinic acid and under the guise of alkaline hyperdiuresis. The dosage of blood MTX-HD may be useful in carrying out this therapy.

MTX –HD TDM

Actualy, TDM of this drug is routinely performed to adjust the dose of folinic acid secondarily administered to limit the risk of MTX-toxicity.

The individual dose adjustment of folinic acid depends on several criteria such as the type of cancer, adults or children, concentration of MTX, hours of samples. Different therapeutic protocolsof folinic acid posology are adopted. The most used in LAL are the GRAALL (Table3) [62] and EORTC protocols in adult and children, respectively. These treatment strategies differt by the dose of folinic acidajusted according the MTX concentration level. We noted that the acid folinic dose are calclated according to BSA. Anyway, the level of MTX concentration allowing the end of folinic acid treatmentis <0.2 µmol/l in both adults and children. In the malignant lymphomas B, the protocol of folonic acid use is the BURKITT protocol in both adult and children. MTX dosing should be continued until the MTX concentration level < 0.15 µmol/l [63].

Table 3: Adjustment of folinic acid doses level and administration time of Methotrexate in LAL adults patients according to therapeutic recommendation « GRALL » 2005

	Methotrexate level (µmol/l)					
T/Methotrexate	**< 0.2**	**0.2 – 0.5**	**0.5-1**	**1 - 5**	**5 - 10**	**> 10**
H 36	-	25 mg x 4	25mg x 4	25mg x 4	25mg x 4	25mg x 4
H 48	-	25 mg x 4	25mg x 4	25mg x 4	25mg x 4	100 mg x 4
H 72	-	25mg x 4	25mg x 4	100 mg x 4	200 mg x 4	400 mg x 4
H 96	-	25mg x 4	100 mg x 4	200 mg x 4	400 mg x 4	400 mg x 4
>H 96	-	100mg x 4	200 mg x 4	400 mg x 4	400 mg x 4	400 mg x 4

T : time since The start of MTX infusion, MTX : Methotrexate level in µmol/l

This practice is provided for in the most curent protocols using MTX-HD, and the dosage is largely used. The aim of TDM MTX-HD is to early discover patients in whom drug clearance is delayed and who are therefore at increased risk of toxicity. in the routine, the measurement of the concentration of TMX in biological samples such as plasma, serum and / or whole blood is done by the immunoassay technique, although chromatographic assays have been developed [64], Clinical result interpretation and consequent adjustment of dosage regimes are based on the dosing protocols already described [65].

MTX-HD exposure-toxicity relationships

TDM MTX-HD is necessary seen that the importance of inter-individual pharmacokinetic variability. As seen as the therapeutic range, ie the range between the effective concentration and the toxic concentration, of MTX is very narrow. On the one hand, it allow to know the concentrations in the blood concentration and to understand the kinetics elimination of MTX-HD, on the other hand, it helps to control and modify the rescue either by adapting the doses of folinic acid and the modalities of alkaline hyperhydration. TDM MTX-HD is essentially based on measurements of concentration at a time (hours) which takes into account the start of the infusion. These times are described by the clinical protocol in the patient and which are :36h, 48h, 72h and 96 h.

Indeed, most of the MTX-HD administered dose is found unchanged in the urine (60%-90%) and 1 to 10% in the form metabolized to 7-hydroxy-methotrexate. The rest is eliminated by bile and faeces.

Alkalization of urine is made to facilitate the extraction of MTX and avoid its intratubular precipitation, since 7-hydroxy-MTX, a very weak metabolite, inhibits the renal excretion of TMX by competition which induces a risk of precipitation of this agent in the renal tubules causing an increase in nephrotoxicity. Several studies have looked for a link between the level of individual exposure and toxicity. The results obtained are interpreted according to different treatment protocols (infusion modalities : dose and time), type of cancer, etc. [65,67,68]

The first studies which were made, in adult and child patients, showed that the infusion of a dose of 2 to 10 g / m^2 in short infusion of 6 hours to generate a development of a toxicity in 42%. This toxicity is explained by a delay in elimination of this agent and therefore a persistence of a measurable concentration greater than 0.9 µM at 48 hours for more than 5 to 6 days. These observations have led to the threshold at risk of toxicity at 48h which is equal to 1 µM [68]. Other studies determined the concentrations of MTX which correspond to the threshold values associated with the risk of toxicity, in patients receiving 8g / m^2 and 12g / m^2 by infusion of 4 h, were 10 µM at 24 h, 1µM at 48h and 0.1µM at 72h [66,68,69]. In children receiving a dose of 4.87 g / m^2MTX in 4 hours for osteosarcoma, the concentrations measured at 24 hours showed an association between the risk of nephrotoxicity and serum creatinine and the concentrations measured at 24 hours after the end of the infusion. Indeed the higher concentrations at 3.5 µM had twice the risk of nephrotoxicity as well as increased hematotoxicity. Likewise, the Cmax at the end of the infusion (infusion of 6 hours) greater than 10^{-3}M would be correlated with a probability higher tumor response and free survival time relapse (Masson, n.d.). In the case of a 24-hour prolonged infusion for acute LAL, studies have shown that patients with a concentration greater than 1µM and /or greater 0.5µM 48 hours after the start of the infusion,

exhibited toxicity [61,69,70]. This observed toxicity is possibly explained by drug interaction especially substances which cause the re-establishment of the binding of MTX to albumin such as non-steroidal anti-inflammatory drugs (NSAIDs) (especially ketoprofen), salicylates, antibiotics of the aminoglycoside class, pristinamycin and especially trimethoprim-sulfamethoxazole which must not be combined with MTX. TDM of MTX, with a consequence of the implementation of hyperhydration and folinic acid rescue measures, helps to limit the incidence and / or severity of toxic manifestations during MTX-HD treatment [61,71].

Level evidence of MTX-HD

The TDM MTX-HD is the subject of general consensus and is recommended for monitor toxicity in order to adapt corrective measures following expressed overexposure [61]. These measures are part of the management of patients receiving this agent. These for that the effectiveness has not been proven by prospective randomized studies which are currently becoming impossible as the application of these measures is universal.

Platinum Salts

PSs activities

Platinium salts (PSs) (cisplatin, carboplatin, oxaliplatin) are one of the major cytotoxics chemotherapy for the management of ovarian, colorectal, and other solid tumors. Cisplatin was the first of the platinum drugs to be used. Carboplatin, an analog of cisplatin, has often been used in place of cisplatin because of a lower incidence of nephrotoxicity and neurotoxicity.

The cytotoxicity of platinum agents is exerted through different cellular mechanisms. Platinum salts primarily act by damaging cellular targets inducing direct or indirect DNA alterations, and cytoplasmic proteins modifications. PSs are capable of binding to DNA by attaching an alkyl group on a guanine base, at the nitrogen of the purine ring [72]. The formation of the DNA adduct (DNA-platinum complex) inhibits DNA repair, transcription and replication by blocking the progression of replicating enzymes along the molecule which induces appoptosis of cancer cells and a increased oxidative stress in cells [73]. These events lead to cell death by apoptosis or necrosis. Apoptosis is executed by a series of cysteine proteases, termed caspases. Caspase activation leads to mitochondrial dysfunction and DNA fragmentation. Cytotoxicity is thus dependent on the amount of platinum bound to DNA [74].

Platinum salts are long-standing compounds used in several cancer types, but each PSs has its own spectrum of activity and toxicity which is due to their chemical structural differences. This difference justifies the diversity of their clinical indication [75]. In addition, several side-effects dose-dependent toxicities were reported such myelosuppression, nausea and vomiting, nephropathy, neuropathy, ototoxicity, reduced fertility, persistent neuropathy, and secondary malignancies. As for most anticancer agents, these toxicities have often limited the use of optimally effective doses, so the importance of therapatic drug monotiring. However PSs are administered by short intravenous infusions every 3 weeks in a specific cycle. Therefore the concentration of these agents is determined only at the end of the administration, which rounds any dose adjustment for the current cycle very difficult. It is for this reason that TDM for platinum salts is not systematically practiced. Some authors having suggested that a single measurement of plasma platinum concentration could be enough for estimating area under curve (AUC) of free platinum.

Cisplatin

Pharmacokinetic interindividual variability

Cisplatin is an anticancer agent widely used in testicular cancer, for which pharmacokinetic (PK)/pharmacodynamic relationships have usually been based upon measurement of its free plasmatic fraction. Because it has been shown that free Cisplatin clearance can be related to patient's body surface area, dosage is mostly adjusted a priori using only this single parameter, with mixed results for accurately predicting cisplatin exposure and reducing toxicities. Because the impact of Cisplatin exposure levels on both toxicity and response is now well established, developing strategies to ensure controlled systemic drug exposure to reduce PK and pharmacodynamic (PD) interpatient variability, subsequent occurrence of toxicities, and to optimize clinical outcome in cancer patients, is an ongoing issue in clinical oncology [76]. The severe toxicity of cisplatin has been shown to was correlated with the administration schedules of this chemotherapy agent and also with the pharmacokinetics of total platinum. Cisplatin is contraindicated in patients with impaired renal function, to avoid further deterioration of renal function given its nephrotoxic effects [77]. However, the toxicity of cisplatin exhibits a large interindividual variability which depends on the administration schedules, the reference

protocol of which is to combine cisplatin with 5-fu and docetaxel or cetuximab. Several dosing strategies have been developed to yield the optimal Cisplatin exposure with minimal toxicity. One of the best administration schedules is the protracted infusion [78].

PK/toxicity relationship

This choice depends on the patient and the renal function. Several studies have shown a correlation between the PK / PD relationship and drug exposure to toxicity and / or efficacy parameters. These studies have well described the relationship between cisplatin PK and toxicity. The preferential marker of exposure is AUC of which their level depends on the administered dose of a drug and the elimination capacity (clearance). The pharmacokinetics of the platins is explored in plasma ultrafiltrates instead of total plasma concentrations. Several studies have shown that the nephrotoxicity observed following administration of cisplatin was correlated with ultafiltred plasma concentrations (Cmax) and the AUC (r^2= 0.83; p<0.0001) [79-81]. A correlation has been proven between Cmax of ultrafiltrable plasma, at the end of 80mg/m^2 cisplatine perfusion, and significant decrease of creatinine clearance after four cycle of cisplatine (r^2= 0.73 ; p < 0.005) [81]. In fact, the duration of infusion of the same dose of cisplatin is not a factor that can influence renal function differently [82]. The data in this direction are controversial since there are studies which show that the administration of this agent for a long duration (more than 72h) involves a risk of reduced nephrotoxicity also it allows the doing of intra-cycle TDM [83]. The 5-day cisplatin infusion allows dose adjustments on days 4 and 5 with varying degrees of precision (6% : precision between actual and target Cmax) to achieve a maximum target concentration of total cisplatin (Cmax) of 1.95 µg / ml [84] (Table 2). However, TDM in a standard protocol (an infusion of a dose of 80 to 100 over a short period of 1 hour to 3 hours) is based on the patient's tolerance, regardless of whether they are adults or children [80]. Whereas, in the case of nephrectomy or dialysis, TDM is based on a dose reduction of 30 to 50% or dose-escalating approach to reach optimal dose [85].

This adjustment of the cisplatin dose is useful in anticipating its nephrotoxicity by measuring, by HPLC, the maximum concentration of free or total platinum. Despite promising published results, the data to agree firm recommendations for TDM are very limited (Table 2). In clinical practice, in order for TDM cisplatin to be recommended, one should measure the peak concentration (Cmax) at end of infusion and at long-term protocols and use Bayesian models for dose adjustment [79].

Carboplatin

Individual dosing of carboplatin

This molecule is better stabilized in plasma compared to the cisplatin molecule thanks to its decarboxylate ligand. This difference between these two plates implies significant changes in the physicochemical properties and it leads to a significant pharmacokinetic variation and consequently to individualization of the doses [86]. Several strong elements can justify the TDM of carboplatin such as the great interindividual variability of carboplatin and the dose-dependent hematological toxicity its consists of thrombocytopenia when administered as monotherapy, and neutropenia associated with thrombocytopenia in combination with other cytotoxics [11].

It is given intravenously as a short infusion (usually 30 minutes or 1 hour), most often as a combination chemotherapy. Individual adjustment of carboplatin dosage is commonly performed on the basis of renal function specifically on free clearance. The dose of carboplatin was individualized for each patient according to a pharmacological therapeutic monitoring strategy.

Otherwise from the changes in renal function already mentioned, inter- and intra-individual variations are also linked to factors of the patient such age, sex, weight [87]. Individual dose adjustments are necessary in order to improve the therapeutic index of carboplatin alone or in association. They are based on the estimate of the patient's renal function and / or the estimate of the AUC of the ultrafilterable plasma from a limited number of samples plasma. The intervariability is better correlated with AUC of the ultrafilterable carboplatin plasma than the dose, the relationship between AUC and antitumor activity [88].

PK/PD relationship of Carboplatin

The toxicity (myelosuppression) observed on carboplatin was correlated with the systemic exposure of carboplatin expressed by AUC which exceed 5 to 7 mg.min/ml. Indeed, the study by Jodrell et al., has shown this relationship between its AUC and the toxicity of carboplatin in 1028 patients with advanced ovarian cancer on monotherapy receiving 40 to 1000 mg / m^2 of this agent. This increase in dose as it induces a myelo-

toxicity which continues to increase with AUC it also induces efficacy with an AUC of 5 to 7 mg.min/ml [89] (Table 2).

When administered with etoposide the effect of carboplatin on thrombocytopenia was multiplied by 1.45 times and it is 2.33 times with gentamicin, these toxicities are observed with an elevation of AUC of ultrafiltered carboplatin. Contrariwise the effect of carboplatin decreases by 0.76 times when combined with paclitaxel therefore it generates a protective effect [11,90].

Carboplatin is a remarkable example of a drug whose exposure/ efficacy relationships have been well-studied. The data obtained from these studies made it possible to define a target AUC interval, in adults and children, in order to optimize the efficacy and control the toxicity [91,92].

Several authors have sought a formula for calculating the dose of carboplatin to achieve optimal AUC. This formula was in the form : Dose = CLpredicted X AUCtarget (Calvert formula) [93]. Knowing that the main route of elimination of carboplatin is through the kidneys. Indeed, within 24 hours of the administered dose, approximately 55 to 70% of the administered dose of carboplatin is excreted in the urine by glomerular filtration [1,94]. AUC of carboplatin and pharmacodynamics have been well documented [1,61,91-93]. For a standard protocol given, it is therefore necessary to define a target AUC and to provide the means to predict clearance [95]. In general, a target AUC is chosen based on chemotherapy regimens. In intensification protocols with high-dose, AUC of 24 mg.min/mL is set as target to be achieved over 3 days with a daily AUC of 8 mg.min/mL per day [90,96]. This AUC target is based on the hypothesis that carboplatin clairance was constant over the 3 days of the cycle. If major ototoxicity was not observed for subsequent cycles of treatment, the AUC of 24 mg.min / mL remained as AUC target, otherwise, the AUC target was reduced to 8 mg.min / mL. In clinical practice, an initiation with a reduced AUC target is made, then it will be increased depending on the patient's tolerance. For the 3-day/ cycle carboplatin administration schedule, the dose adjustment is made on day 2 or on day 3, it is based on drug exposures and on the clearance values already determined on day 1 and / or day 2, in order to reach the AUC target [84]. These adjustments have been recommended for patients whose AUC exceeds 10% of the AUC target and were calculated based on the remaining AUC to be reached and actual carboplatin clearance determined on day 1. These parameters (Clearance and AUC) of carboplatin were determined by a population pharmacokinetic model allowing a reliable estimate. Clearances of carboplatin vary from adults, pediatrics and neonates pattern according to several covariates such as weight, age, the glomerular filtration rate. This letter is the creteria for predicting carboplatin clearance of each patient [1,97]. In subsequent cycles, the carboplatin treatment is guided by the data observed in the first cycle with TDM performed as appropriate. In the context of intensification protocols, carboplatin TDM is potentially useful by measuring AUCs as a function of free platinum. AUC measurement and use of Bayesian dose adjustment models determined and validated to demonstrate carboplatin TDM.Indeed, there is still no strong evidence of clinical benefit of TDM, either in terms of efficacy or toxicity [79].

Oxaliplatin

Oxaliplatin is a drug that occupies the middle positionbetween cisplatin and carboplatin. Similarly to cisplatin, the main mechanism of action of oxaliplatin is mediated through the formation of DNA adducts who are capable of blocking both DNA replication and transcription, they are considered the major cytotoxic lesions [98]. Oxaliplatin causes adverse reactions that narrow its therapeutic index. The target organs are mainly the hematopoietic system, the peripheral nerves (50% of patients at 135 mg/m^2, 64% at 150 mg/m^2, 71% at 175 mg/m^2, and 100% at 200 mg/m^2), and the gastrointestinal system.

On the basis of the criterion of an "intermediary" it has interindividual variability comprised between those of the other two compounds. The data in the literature are controversial in the case of dose adjustment. Some studies propose adaptation methods based on clearance and others which report that the dose of oxaloplatin does not depend on renal function and that the elimination of this agent is moderate knowing that its renal clearance corresponds to approximately 40 % of total clearance. In patients with moderate renal impairment dose adjustment is not necessary while with severe renal impairment recommendations differt. The information FDA prescription recommends a reduction in the dose of oxaliplatin from 85 to 65 mg / m2 in those patients with creatinine clearance <30 mL / min [99], (Table2), whereas this is contraindicated in the summaries European Product Characteristics (SPC) [1]. In cancer patients undergoing hemodialysis, this medicine is contraindicated because renal failure strongly modifies its pharmacokinetics [85]. However, when its indication is mandatory, a reduced dose (from 30 to 50%) or an increasing dose should be administered initially but after hemodialysis in order to treat these cancer patients ef-

fectively with monitoring [100], with oxaliplatin by simultaneously monitoring total and / or free Pt PK concentrations [101].

Etoposide

Indication

Etoposide is a chemotherapy treatment, which acts by the inhibition of topoisomerase II (nuclear enzyme) which induces the blocage of total cell cycle in the G2 phase. This drug is widely used in the treatment of a variety of solid neoplasm's, such as lung and testicular cancer. It is prescribed in monotherapy or in combination with other anticancer drugs, especially cisplatin [101]. Moreover, it is indicated as conditioning chemotherapy before hematopoietic stem cell transplantation in adult and pediatric patients, administered at high doses. In adults, the recommended dose of etoposide is 50 to 100 mg / m2 / day on days 1 to 5 or 100 to 120 mg / m2 on days 1, 3 and 5 every 3 to 4 weeks, in combination other drugs indicated in the disease to be treated. In the pediatric population, the recommended dose varies from 75 to 150mg/m2/day for 2 to 5 days [103].

Pharmacokinetic activity

Several studies have shown significant interindividual variability of etoposide clinical response [95] Indeed, It has demonstrated that a plasma concentration value (Cmin) at steady state (C_{SS}) above 1µg/ml is associated with optimal efficacy response, i.eantitumor activity (efficacy) in both lung and testicular cancer. In another hand, a positive correlation between high drug exposure; i,e, Cmin, and toxic side effects; i.e, hematological toxicity, infection, fever, has been previously documented. Indeed, Ratain et al and Miller et al have shown that Cmin values above 2 µg/ml and 3 µg/ml, respectively, are associated to the occurrence of etoposide toxic side effects (Cmin > 0.3 mg/L is associated with grade3 and 4 neutropenias) [104-106]. Thus, in order to ensure the efficacy and prevent toxicity, previous studies focused on etoposide-TDM proposed a concentration target range between 1µg/ml and 3µg / ml. Moreover, some studies found a significant correlation between AUC of etoposide and overall patient survival [107]. The 30 min infusion of a 120 mg / m2 dose of etoposide over 3 days in combination with the platinum derivatives gave a significant correlation between the clearance of etoposide (≤ 2.22 L / h) and l 'AUC (> 254.8 mg.h /L) with longer overall survival. The etoposide dose adjustment is based on the condition of patients. It is recommended in situations where the risk increase in the free fraction is significant because the pharmaco logical effects of etoposideare better related to exposure to the free fraction than to total exposure [108]. For exemple, in severe renal impair mentor liver failure. A reduction dose of around 30% could correct increasing AUC to achieve a similar level of exposure to patients with normal renal function. Whereas, if the oral administration of a 100mg / day dose for 14 days and 21 daysevery 4 weeks, the TDM is based on the determination of the trough concentration after 24 h of administration. Studies have shown a significant association between the value of C min (≥1.49 mg / L) and the lowest level of granulocytes and platelets [109]. The measurement of these concentrations was based on HPLC methods with UV or fluorescence detection [110]. It was based on measuring the concentration at steady state allows the dosage to be adjusted for the current cycle, but also for the following cycles, because the variability intra-individual is low [111]. The concentration-effect (efficacy or toxicity) relationships of etoposide depend on the administration schedule regardless of oral administration for 21 days or by infusion over a few days. These relationships are well documented. Limited studies have shown the relationship between the effectiveness of treatment, intravenously, and the duration of treatment.

These studies compared the effectiveness of two administration schedules, in patients with small cell lung cancer, by an IV infusion over 24 hours as a single dose versus an IV infusion over 2 hours over 5 consecutive days (usual schedule). They showed that the duration of exposure to etoposide concentration> 1 mg / L was associated with anti-tumor activity [112]. During TDM, clinicians begin their orally treatment regimen with an initial dose of 75 mg (one 25 mg capsule / 3 times daily) to achieve the target concentration range of 1.0 to. 1.5 µg / ml. From the 5th day the dose was modified by lowering the dose to 50 mg per day (25mg / 2 times) or by increasing this dose up to 100mg per day, depending on the mean of the trough concentrations obtained on day 3 and 4. These concentrations wascalculated by use of a limited sampling model that makes TDM applicable to oral etoposide [113].

In this context, dose adjustment has beenevaluated by population pharmacokinetic models, that allow dose adjustment duringcontinuous infusions as a function of haematological toxicity, particularly neutropenia. The advantages of these models are to reduce pharmacokinetic variability and increase the dose intensity compared to the fixed dose regimen [103].

In summary, studies have shown a correlation between exposure and toxicity, especially haematological toxicity, but data regarding the correlation between exposure and efficacy are less complete and limited. The use of controlled concentrations and dose adjustment help reduce inter-individual variability and haematological toxicity. The level of evidence for oral etoposide TDM is "potentially useful" as further reduction in variability. Non-randomized studies have shown only an improvement of efficacy variabilityand not in terms of security (toxicity). All these arguments available in the literature indicate that etoposide TDM is recommended.

Conclusion

In this review, we have discussed the interest of TDM of certain anticancer drugs by studying the relationships and relationships between exposure (AUC) and response (especially toxicity) and clinical experiences with TDM of these agents. Analysis of data from large randomized clinical trials, which evaluate the use of TDM, showed levels of evidence for these drugs. Unfortunately, the routine application of TDM of this therapeutic class is very limited although these anticancer drugs are characterized by interindividual variability and a stellar therapeutic index. The limited use of this strategy can be explained on the one hand by the lack of population pharmacokinetic data of these anticancer agents and also the lack of target concentration. On the other hand, the analytical difficulties encountered, such as the difficulties of measuring active metabolites, and the cyclic administration regimens whose adaptation is no longer possible for the current cycle but for the next cycle. Generally the dosage adjustment of these anticancer drugs is carried out on the basis of the observation of toxicity. in the future, efforts should be made on the TDM of anticancer drugs to optimize the dosing protocol by increasing the therapeutic utility of oncologic therapies and achieve to deliver the right anticancer in the right dosage to the right patient in the adjustment of routine. In fact, it is wrong to better determine the kinetics of these agents and place the exposure-effect relationships through the development of new TDM tools and the performance of dominated trials which are interested in the evaluation of clinical benefit.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Declaration of Interest

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

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