Advances, possibilities, and challenges of anti-cancer chemotherapy and the utilization of therapeutic drug monitoring to improve outcomes :State of the Atr

TESFAYE H

Division of Clin Pharmacol.,Dept Med Chem &Clin Biochem University Hospital Motol, 2nd Faculty of Medicine, Charles University, Prague , CZECH REPUBLIC

e-mail:hundie.tesfaye@fnmotol.cz

Abstract: - Therapeutic drug monitoring (TDM) have been applied most frequently in the cardiovascular, respiratory, neurology, and infectious disease areas because the medications used have both narrow therapeutic indices and marked interindividual variability with clear relationship between concentration and effect. However, Therapeutic drug monitoring is not routinely used for chemotherapy agents till recently, when target concentration or exposure measure such as AUC have been established in clinical practice for the optimization of drug treatment, apart from drugs such as methotrexate and 5-fluorouracil. Several factors including poorly defined concentration-effect relationships limit the use of therapeutic drug monitoring (TDM) for many cancer chemotherapeutic/antineoplastic agents. This is further complicated by cancer being a highly heterogeneous group of diseases, each of which may have a unique concentration-effect relationship for any given drug or drug combination. Defining concentration-effect relationships is also complicated by the fact that cancer is almost always treated with multiple drugs given in combination making the precise definition of the pharmacodynamics of individual agents difficult. Nonetheless, TDM clearly has the potential to improve the clinical use of antineoplastic agents, most of which have very narrow therapeutic indices and highly variable pharmacokinetics. There is also a substantial body of literature demonstrating relationships between systemic exposure to various chemotherapy agents and their toxic or therapeutic effects. Furthermore, in the last decades, relationships between plasma drug concentrations and clinical outcome have been defined for various chemotherapeutic agents. The **objective** of this contribution is to describe some of the evidence that support the use of TDM in oncology ,while emphasizing the shortcomings and challenges related unless extremely cautioous interpretation and individualized approach is applied. The final **take home message** is also to propose that TDM may play a critical role in optimizing chemotherapy outcomes if wisely used with continious knowledge based pharmacokinetic-pharmacodynamic research results upplied by multidisciplinary team of professionals.

Key-Words: - Cancer therapy, Toxicity challenges , drug safety, theraputic drug monitoring

1 Introduction

Several anticancer drugs display characteristics that make them suitable candidates for therapeutic drug monitoring (TDM), including substantial pharmacokinetic variability and a narrow therapeutic index. However, concentration-effect relationships (pharmacodynamics) of most antineoplastic agents have not been well defined, thus limiting the widespread clinical application of TDM for cancer chemotherapy. Strategic incorporation of pharmacokinetic studies during phase I-III clinical trials should facilitate the identification of concentration-effect relationships and the definition of clinically useful levels of treatment intensity. We review representative clinical studies that have defined pharmacodynamic relationships for methotrexate, teniposide, etoposide, carboplatin, and mercaptopurine. Given that TDM has impacted positively on the clinical use of many drugs belonging to other therapeutic classes, and that pharmacodynamic correlations have been identified in several recent studies of anticancer drugs, we consider

implementation of TDM a rational strategy for optimizing the use of selected antineoplastics.[1] There is cummulative evidence that Therapeutic drug monitoring provides valuable guidance for dose adjustment of antibiotics, immunosuppressives, antiepileptics, and other drugs, but its use for traditional anticancer therapies has been limited till recently. Perhaps the most important obstacle is the impractical requirement of multiple blood samples to adequately define systemic exposure of drugs that have a short elimination half-life and are given by intermittent intravenous injections. However, the newer targeted anticancer therapies have different pharmacokinetic (PK) and dosing characteristics compared with traditional cytotoxic drugs, making it possible to estimate the steady-state drug exposure with a single trough-level measurement.Recent evidence indicates that certain PK parameters, including trough levels, are correlated with clinical outcomes for many of these agents, including imatinib, sunitinib, rituximab, and cetuximab. Although the current evidence is insufficient to mandate TDM in routine practice, a concerted investigation should be encouraged to determine whether the steady-state trough measurements of targeted agents will have a practical place in the clinical care of patients with cancer.[2] Therapeutic drug monitoring (TDM) is increasingly used in clinical practice for the optimisation of drug treatment. Although pharmacokinetic variability is an established factor involved in the variation of therapeutic outcome of many chemotherapeutic agents, the use of TDM in the field of oncology has been limited thus far. An important reason for this is that a therapeutic index for most anticancer agents has not been established; however, in the last 20 years, relationships between plasma drug concentrations and clinical outcome have been defined for various chemotherapeutic agents. Several attempts have been made to use these relationships for optimising the administration of chemotherapeutics by applying pharmacokinetically guided dosage. The prospective studies, individualising chemotherapy dose during therapy based on measured drug concentrations, and review focusing on the way a target value is defined, the methodologies used for dose adaptation and the way the performance of the dose-adaptation approach is evaluated. Furthermore, attention is paid to the results of the studies and the applicability of the strategies in clinical practice enables to conclude that TDM may contribute to improving cancer chemotherapy in terms of patient outcome and survival and should therefore be further investigated.[3] For a select number of drugs, proper management of patients includes monitoring serum or plasma concentrations of the drugs and adjusting the doses accordingly - this practice is referred to as therapeutic drug monitoring (TDM). The need for TDM arises when pharmacokinetic variability of drugs is not easily accounted for by common clinical parameters. Many chemotherapeutic drugs have large interindividual variability, yet TDM is not commonplace in chemotherapy management. This review will discuss pharmacokinetics in the context of chemotherapeutic drugs, examine the few instances where TDM is currently used in the field of oncology and propose other drugs where TDM might be useful for dose adjustments in the management of chemotherapy. [4]Therapeutic drug monitoring is not routinely used for chemotherapy agents. There are Several reasons, but one major drawback is the lack of established therapeutic Concentration ranges. Combination chemotherapy makes the establishment of Therapeutic ranges for individual drugs difficult, the concentration-effect relationship for a single drug may not be the same as when that drug is used in a drug combination. Pharmacokinetic optimization protocols for many classes of cytotoxic compounds exist in specialized centers, and some of these protocols are now part of large multicentre trials. Nonetheless, TDM clearly has the potential to improve the clinical use of chemotherapy gents, most of which have very narrow therapeutic indices and highly variable pharmacokinetics. A substantial body of literature accumulating during the past years demonstrates relationships between systemic exposure to various chemotherapy agents and their toxic or therapeutic effects.[5] Hoever, therapeutic drug monitoring is not routinely used for cytotoxic agents. There are several reasons, but one major drawback is the lack of established therapeutic concentration ranges. Combination chemotherapy makes the establishment of therapeutic ranges for individual drugs difficult, the concentration-effect relationship for a single drug may not be the same as that when the drug is used in a drug combination. Pharmacokinetic optimization protocols for many classes of

cytotoxic compounds exist in specialized centres, and some of these protocols are now part of large multicentre trials. Nonetheless, methotrexate is the only agent which is routinely monitored in most treatment centres. An additional factor, especially in antimetabolite therapy, is the existence of pharmacogenetic enzymes which play a major role in drug metabolism. Monitoring of therapy could include assay of phenotypic enzyme activities or genotype in addition to, or instead of, the more traditional measurement of parent drug or drug metabolites. The cytotoxic activities of mercaptopurine and fluorouracil are regulated by thiopurine methyltransferase (TPMT) and dihydropyrimidine dehydrogenase (DPD), respectively. Lack of TPMT functional activity produces life-threatening mercaptopurine myelotoxicity. Very low DPD activity reduces fluorouracil breakdown producing severe cytotoxicity. These pharmacogenetic enzymes can influence the bioavailability, pharmacokinetics, toxicity and efficacy of their substrate drugs.[6] In fact several anticancer drugs display characteristics that make them suitable candidates for therapeutic drug monitoring (TDM), including substantial pharmacokinetic variability and a narrow therapeutic index. However, concentration-effect relationships (pharmacodynamics) of most antineoplastic agents have not been well defined, thus limiting the widespread clinical application of TDM for cancer chemotherapy. Strategic incorporation of pharmacokinetic studies during phase I-III clinical trials should facilitate the identification of concentration-effect relationships and the definition of clinically useful levels of treatment intensity. We review representative clinical studies that have defined pharmacodynamic relationships for methotrexate, teniposide, etoposide, carboplatin, and mercaptopurine. Given that TDM has impacted positively on the clinical use of many drugs belonging to other therapeutic classes, and that pharmacodynamic correlations have been identified in several recent studies of anticancer drugs, there is consideration for implementation of TDM a rational strategy for optimizing the use of selected antineoplastics.[7] Over the last decades, proofs of the clinical interest of therapeutic drug monitoring (TDM) of certain anticancer drugs have been established. Numerous studies have shown that TDM is an efficient tool for controlling the toxicity of therapeutic drugs, and a few trials have even demonstrated that it can improve their efficacy. This article critically reviews TDM tools based on pharmacokinetic modelling of anticancer drugs. The administered dose of anticancer drugs is sometimes adjusted individually using either a priori or a posteriori methods. The most frequent clinical application of a priori formulae concerns carboplatin and allows the computation of the first dose based on biometrical and biological data such as weight, age, gender, creatinine clearance and glomerular filtration rate. A posteriori methods use drug plasma concentrations to adjust the subsequent dose(s). Thus, nomograms allowing dose adjustment on the basis of blood concentration are routinely used for 5-fluorouracil given as long continuous infusions. Multilinear regression models have been developed, for example for etoposide, doxorubicin. carboplatin, cyclophosphamide and irinotecan, to predict a single exposure variable [such as area under concentration-time curve (AUC)] from a small number of plasma concentrations obtained at predetermined times after a standard dose. These models can only be applied by using the same dose and schedule as the original study. Bayesian estimation offers more flexibility in blood sampling times and, owing to its precision and to the amount of information provided, is the method of choice for ensuring that a given patient benefits from the desired systemic exposure. Unlike the other a posteriori methods, Bayesian estimation is based on population pharmacokinetic studies and can take into account the effects of different individual factors on the pharmacokinetics of the drug. Bayesian estimators have been used to determine maximum tolerated systemic exposure thresholds (e.g. for topotecan or teniposide) as well as for the routine monitoring of drugs characterized by a very high interindividual pharmacokinetic variability such as methotrexate or carboplatin. The development of these methods has contributed to improving cancer chemotherapy in terms of patient outcome and survival and should be pursued.[8] High-dose busulfan is an important component in many conditioning protocols for hematopoietic stem cell transplantation (HSCT) or bone marrow transplantation (BMT) in both adults and children. During the past 12y several studies have reported the wide inter-individual variability in busulfan disposition. Age, disease status, hepatic function, circadian rhythmicity,

drug interactions and bioavailability, were identified as factors contributing to the high inter-individual variability found in busulfan disposition. Traditionally, a standard busulfan dose of 4mg/kg/d for four days is used in most BMT/HSCT protocols. Many investigations have pointed out the pharmacodynamic relationship between a high busulfan systemic exposure and the occurrence of BMT related toxicity including hepatic veno-occlusive disease (VOD), interstitial pneumonia and alopecia in adult patients. However, studies in young patients have shown a high rate of graft failure and subsequently relapse which most probably is due to the low systemic exposure despite the standard dose schedule. In children and infants VOD was not observed with the standard doses. Increasing interest for the drug and new modification strategies for children led to higher rate of VOD and CNS toxicity when busulfan was administered according to the body surface area. More pharmacodynamic studies are advised to establish the relation between the systemic exposure to busulfan and the therapeutic efficacy, especially in young children undergoing BMT or HSCT. In the present time an accurate and effective busulfan plasma level monitoring combined with dose adjustment based on the known pharmacological parameters may improve the clinical outcome for patients undergoing bone marrow transplantation.[9] Methotrexate (MTX) at a dose of ≥1 g/m(2) remains the most efficient treatment against primary central nervous system lymphoma (PCNSL), and is the most widely used drug in prospective clinical trials. MTX is a folate analog that inhibits dihydrofolate reductase, thereby blocking de novo purine synthesis. MTX as well as 7-hydroxy-MTX, its main metabolite in serum, are both eliminated by the kidneys. The elimination of MTX is prolonged in patients with renal impairment and third-space fluid collections, and in patients receiving concurrent non-steroidal antirheumatic drugs, benzimidazoles and sulfonamides, among others. Main adverse events with high-dose MTX include severe myelosuppression, renal dysfunction and stomatitis. Supportive measures such as rigorous hydration, urine alkalinization and careful drug monitoring with supplemental leucovorin rescue are crucial to avoid significant toxicity. Strategies to optimize clinical efficacy of high-dose MTX in patients with PCNSL include administration of 3 h instead of longer infusions, potentially supplemented with an additional intravenous MTX bolus, and maintaining MTX dose intensity over the course of four treatment cycles. Some pharmacological studies suggest that achieving an MTX area under the plasma concentration-time curve (AUC(MTX)) of between 1000 and 1100 μmol.h/L may improve clinical outcome, but clinical data are not conclusive at present. In this review, we analyze the impact of patient, lymphoma and pharmacokinetic variables on the antitumor activity of high-dose MTX in patients with PCNSL, summarize recommendations for daily clinical practice and give some suggestions for future trials.

[10] High dose methotrexate pharmacokinetics and interpatient variability in adults are comparable to those in children. The elimination of methotrexate is not affected by sex or age differences, so that high dose can safely be administered to adults as in younger patients, where a good clinical response can be predicted by C(max), while severe toxicity depends on highest AUC values.[11]

Clearance of creatinine was independently associated with severe toxicity; a significantly higher toxicity rate was observed in patients with a kreatinine clearance 85 ml min−1.

Importantly, a DIMTX >1000 mg m−2/week, and an AUCMTX >1100 μmol h l−1 were not related to a higher toxicity. [12] Methotrexate is the most efficient anticancer drug in osteosarcoma. It requires individual exposure monitoring because of the high doses used, its wide interpatient pharmacokinetic variability and the existence of demonstrated relationships between efficacy, toxicity and serum drug concentrations.The Bayesian adaptive method may allow accurate estimation of individual exposure to methotrexate and can easily be used in clinical practice.[13]

Pharmacokinetics of methotrexate was best described by a 2-compartment open PK model with first-order elimination from the central compartment, while Validation studies confirmed the suitability of the model for further dose individualization by using Bayesian approach.[14]

High dose methotrexate can be administered safely using an adaptive-dosing strategy with drug monitoring, provided that pharmacokinetic modeling enables the accurate prediction of the

methotrexate elimination rate allowing for a better management of the postinfusion care of cancer patients treated with high doses of the drug.[15]

Cecyn et al. reported a case of a 13-year-old girl with osteosarcoma who was treated with high-dose MTX who demonstrated a delayed MTX elimination followed by clinical toxicity recoved after plasma exchange was employed to accelerate MTX removal.[16] In a case of 12-year-old female patient with low-grade right mandibular osteosarcoma, who demonstrated persisting high MXT plasma level only pot one cycle of therapy, significantly fast elmininationafter a single dose of Glucarpidase was observed concluding its safety and effectiveness in the management of high-dose methotrexate-induced nephrotoxicity and delayed methotrexate elimination.[17] Our team have also published a cse of extremely dealayed methotrexate eliminatation in a a yound male pationt with osteosarcoma, where the remedy has been achieved using Glucarpidase.[18]

2 Sientific bases for therapeutic drug monitoring experince in som anticancer drugs

The cytotoxic activities of mercaptopurine and fluorouracil are regulated by thiopurine methyltransferase (TPMT) and dihydropyrimidine dehydrogenase (DPD), respectively. Lack of TPMT functional activity produces life-threatening mercaptopurine myelotoxicity. Very low DPD activity reduces fluorouracil breakdown producing severe cytotoxicity. These pharmacogenetic enzymes can influence the bioavailability, pharmacokinetics, toxicity and efficacy of their substrate drugs.[19] It has been already consider that implementation of TDM could be rational strategy for therapy optimization by to increasing rate of success, while reducing risk of toxicity. at least in selected antineoplastic drugs.[20] Busulfan (Bu)/cyclophosphamide (Cy) is a standard conditioning platform for allogeneic transplantation. We developed a strategy separating the Cy into two pre/post-transplantation doses (PTCy), providing myeloablative conditioning and single-agent graft-versus-host disease (GVHD) prophylaxis. We investigated the impact of Bu route on treatment-related toxicity for 131 consecutive adult patients. Busulfan was administered in four daily divided doses either orally (n = 72) or intravenously (n = 59) with pharmacokinetics on the first-dose and as necessary on subsequent doses to achieve a target area-under-the-concentration-curve (AUC) of 800-1400 μmol*min/L per dose. BuCy/PTCy with pharmacokinetics is well-tolerated with low treatment-related toxicity. Hepatic veno-occlusive disease incidence was 6% with two fatal events. Bu administration route in the context of BuCy/PTCy did not statistically impact hepatotoxicity, GVHD, relapse, disease-free survival, or overall survival. The BuCy/PTCy platform has a low incidence of treatment-related toxicity, including hepatotoxicity, in hematologic malignancies when using pharmacokinetics for a target AUC of 800-1400 μmol*min/L, irrespective of Bu administration route.[21] Personalizing intravenous (IV) busulfan doses in children using therapeutic drug monitoring (TDM) is an integral component of hematopoietic cell transplant. The authors sought to characterize initial dosing and TDM of IV busulfan, along with factors associated with busulfan clearance, in 729 children who underwent busulfan TDM from December 2005 to December 2008. The initial IV busulfan dose in children weighing ≤12 kg ranged 4.8-fold, with only 19% prescribed the package insert dose of 1.1 mg/kg. In those children weighing >12 kg, the initial dose ranged 5.4-fold, and 79% were prescribed the package insert dose. The initial busulfan dose achieved the target exposure in only 24.3% of children. A wide range of busulfan exposures were targeted for children with the same disease (eg, 39 target busulfan exposures for the 264 children diagnosed with acute myeloid leukemia). Considerable heterogeneity exists regarding when TDM is conducted and the number of pharmacokinetic samples obtained. Busulfan clearance varied by age and dosing frequency but not by underlying disease. The authors— group is currently evaluating how using population pharmacokinetics to optimize initial busulfan dose and TDM (eg, limited sampling schedule in conjunction with maximum a posteriori Bayesian estimation) may affect clinical outcomes in children.[22] Most anticancer drugs are characterised by a steep dose–response relationship and narrow therapeutic window. Inter-individual pharmacokinetic (PK) variability is often substantial. The most relevant PK parameter for cytotoxic drugs is the area under the plasma concentration versus time curve (AUC). Thus it is somewhat surprising that therapeutic drug monitoring (TDM) is still uncommon for the majority of agents. Goals of the review were to assess the rationale for more widely used TDM of cytotoxics in oncology. There are several reasons

why TDM has never been fully implemented into daily oncology practice. These include difficulties in establishing appropriate concentration target ranges, common use of combination chemotherapies for many tumour types, analytical challenges with prodrugs, intracellular compounds, the paucity of published data from pharmacological trials and 'Day1 = Day21' administration schedules. There are some specific situations for which these limitations are overcome, including high dose methotrexate, 5-fluorouracil infusion, mitotane and some high dose chemotherapy regimens. TDM in paediatric oncology represents an important challenge. Established TDM approaches includes the widely used anticancer agents carboplatin, busulfan and methotrexate, with 13-cis-retinoic acid also recently of interest. Considerable effort should be made to better define concentration–effect relationships and to utilise tools such as population PK/PD models and comparative randomised trials of classic dosing versus pharmacokinetically guided adaptive dosing. There is an important heterogeneity among clinical practices and a strong need to promote TDM guidelines among the oncological community.[23] Inter-individual PK variability is often large and variability observed in response is influenced not only by the genetic heterogeneity of drug targets, but also by the pharmacogenetic background of the patient such as cytochome P450 and ABC transporter polymorphisms, patient characteristics as well as drug–drug interactions. Retrospective studies have shown that targeted drug exposure, reflected in the area under the plasma concentration–time curve (AUC) correlates with treatment response (efficacy/toxicity) in various cancers. Nevertheless levels of evidence for therapeutic drug monitoring (TDM) are however heterogeneous among these agents and TDM is still uncommon for the majority of them.. Applications for TDM during oral targeted therapies may best be reserved for particular situations including lack of therapeutic response, severe or unexpected toxicities, anticipated drug–drug interactions and/or concerns over adherence treatment for oral treatments.[24] Parenteral busulfan was used in full myeloablative dose and in combination with other drugs; therefore, toxicity rather than underexposure was our main concern. However, clear correlation between AUC and toxicity was not observed. Because of interindividual differences and changes in pharmacokinetics during the busulfan course, we strongly recommend intensive TDM.[25] The over all conclusions drown from our case series and observation was also to recommend inter-dose follow-up therapeutic drug monitoring instead of relaying on initial dose predictions as highly required tool to guarantee aimed target with careful interpretation of drug levels considering all influential factors. Thus, it is strongly suggested that follow-up AUC monitoring between doses may certainly help to reduce the risk of poor outcomes both in adult and paediatric HSCT patients.[26, 27]

Overall emerging evidences show that therapeutic drug monitoring might be mandatory even by utilizing limited sampling strategy (Fig. 1.) in several anti-cancer drugs to improve outcomes..

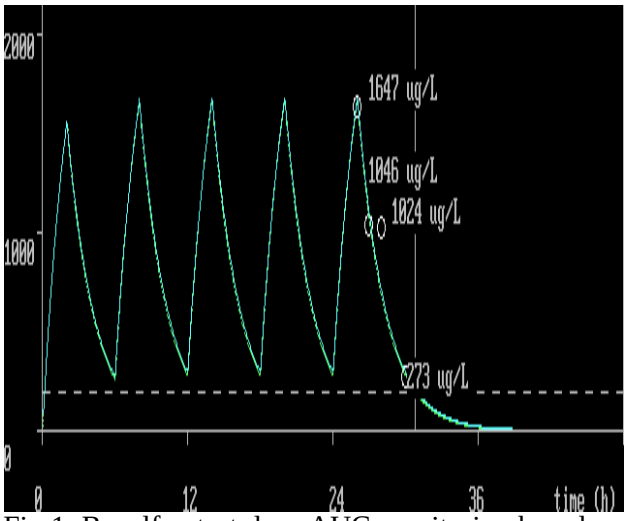
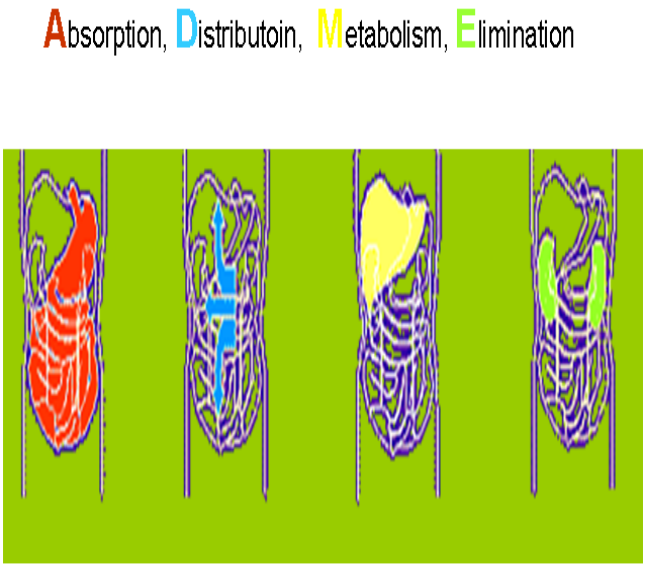


Fig 1. Busulfan test dose AUC monitoring based on four samples demonstrates concentrations(y-axis) in time post dose(x-axis) almost similar concentrations on to consecutive sampling times demonstrating that further sample limitation is possible in high dose busulfan regimen,which maybe most beneficial in paediatric patients requiring more limited sampling strategy in practice.

3 Therapeutic drug monitoring of non-anticancer drugs in cancer patients

Cancer patients are especially prone to drug-drug interactions due to significant comedication, impaired liver and kidney function and hypoalbuminemia with altered drug binding. This article discusses TDM for various broadly used non-anticancer drugs in cancer patients and gives specific recommendations. Selected drugs covered in this article include those regularly used in febrile neutropenic patients such as the glycopeptide antibiotics, aminoglycosides, the antifungal agents, including flucytosine and azole compounds, the

anticonvulsants phenytoin, carbamazepine and valproate, the tricyclic antidepressants, selective-serotonin-reuptake inhibitors, lithium, morphine, digitalis glycosides and the immunosupressants cyclosporin A, tacrolimus, sirolimus and mycophenolate mofetil, crucial compounds in the setting of bone marrow transplantation. In all cases, treating physicians have to consider the variability in patient age, disease stage, comedication, organ function and protein level to weigh the pros and cons of TDM in the individual cancer patient. Drug-Drug interaction problems: may warrant also the importace of the therapeutic drug monitoring in cancer patiens. Several drugs (e.g., penicillin, probenecid) can alter the elimination of methotrexate; While, two cases of delayed elimination of methotrexate in patients receiving ciprofloxacin, with severe toxicity have also been [28] A cording to a case report of delayed elimination of high-dose methotrexate (MTX) associated with concomitant omeprazole administration, omeprazole can inhibit renal elimination of the hydrogen ion and block the active tubular secretion of MTX. Therefore, the elimination half-life of MTX may be increased resulting in potentially toxic concentrations of MTX. At a pH of approximately 5, as found in the renal tubules, pantoprazole is more slowly activated than omeprazole, reducing the incidence of unwanted reactions with sulfhydryl groups and adverse effects occurring outside of the gastric hydrogen pump. [29] Santucci et al. have retrospectively analyzed the causes of delayed methotrexate elimination in patients who had received the rescue agent glucarpidase to evaluate the potential implication of benzimidazoles. The possible causes of delayed elimination identified were: insufficient hydration (n=1) and drug-drug interactions (n=5). The potential drug-drug interactions included the co-administration of piperacillin/tazobactam (n=1) and proton pump inhibitors (omeprazole, n=3; esomeprazole, n=2). Impaired elimination of methotrexate was not observed either in the 3 patients who were treated further or during the previous cycles of the 2 pretreated patients in relation to the absence of co-prescription of proton pump inhibitors.In line with the recent literature and given the prohibitive cost of glucarpidase, the authors have advocated the cessation of proton pump inhibitors administration during methotrexate treatment.[30]



stage namely: A bsorption,Distribution, Metabolism, and Elimination

As one of the big challenges of co-medication and drug-dru interaction in any patient, inparticular in cancer patients can hapen at any stage of pharmacokinetic phases of the drug, including pharmacodynamic interactions both favouable or adverse ones

3.1. Immunosupressant comedications

The use of any immunosupressant agent in oncology patient warants speciál attention.

TDM is commonly used and is vital for avoiding organ rejection and minimising toxicity when drugs like Cyclosporin, Tacrolimus, Mycophenolic Acid, Everolimus are administerd as mono or combination therapy.

. Following an organ transplant intensive TDM is required since the transplanted organ function can change rapidly during the first few weeks.

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), an immunosuppressive agent used in combination with corticosteroids and calcineurin inhibitors or sirolimus for the prevention of acute rejection after solid organ transplantation. Mycophenolic acid glucuronide (MPAG) is the main metabolite of MPA. Although MPA has a rather narrow therapeutic window and its pharmacokinetics show considerable intra- and

interindividual variability, dosing guidelines recommend a standard dosage regimen of 0.5-1.0 g twice daily in adult renal, liver and cardiac transplant recipients.

Musuamba et al. reported that above 50 % of the observed AUC(12) values in patients receiving a fixed dose of mycophenolate mofetil 750 mg twice daily were outside the recommended therapeutic range (30-60 microg x h/mL). The failure of the standard dose to yield an AUC(12) value within the therapeutic range was especially pronounced during the first study period. Of the multiple linear regression models that were tested, the equation based on the 0-hour (pre-dose), 0.66- and 2-hour sampling times showed the best predictive performance in the validation group: r2 = 0.79, relative root mean square error (rRMSE) = 14% and mean relative prediction error (MRPE) = 0.9%. The pharmacokinetics of MPA and MPAG were best described by a two-compartment model with first-order absorption and elimination for MPA, plus a compartment for MPAG, also including a gastrointestinal compartment and enterohepatic cycling in the case of sirolimus co-medication. The ratio of aminotransferase liver enzymes (AST and ALT) and the glomerular filtration rate significantly influenced MPA glucuronidation and MPAG renal excretion, respectively. Bayesian estimation of the MPA AUC(12) based on 0-, 1.25- and 2-hour sampling times predicted the observed AUC(12) values of the patients in the validation group, with the following predictive performance characteristics: r2 = 0.93, rRMSE = 12.4% and MRPE = -0.4%. Use of the developed multiple linear regression equation and Bayesian estimator, both based on only three blood sampling times within 2 hours following a dose of mycophenolate mofetil, allowed an accurate prediction of a patient's MPA AUC(12) for therapeutic drug monitoring and dose individualization, however these findings should be validated in a randomized prospective trial[31] Never theless, the use of any immunosupressant agent in oncology patient warants speciál attention, as imunity is also compromized in thes patients.

3.2. Anti-infectives

Immunosuppression and indwelling IV catheters are much more common, particularly in patients being treated for cancer who are living longer, on more complex chemotherapy regimens, and are more susceptible to infections. Multi-drug resistant bacteria are more common and more patients are coming in contact with them in hospital/nursing home settings – nosocomial infections. Unfortunately recent data from the CORTICUS study found even in patients found to have adrenal insufficiency steroids did not improve mortality [32], but may contribute to further immunosupression. In the study including 8.9 million patients with cancer to evaluate the longitudinal epidemiology of sepsis in patients with a history of cancer and to specifically examine sepsis-related disparities in risk or outcome, it has been concluded that patients with a history of cancer are at increased risk for acquiring and subsequently dying from sepsis, compared to the general population.[33] Thus antibiotics are most frequently used in combination to many tcytotoxic drugs and other complementary medicines in cancer patients. Nephrotoxic antibiotics mainly aminoglycosides and (Amikacin, Gentamicin) and glycopeptides like teicoplanin and vancomycin are used also in cancer patient , who oftenaqire multi-drug resistant infections as aresult of long hospital stay and immunocompromised conditions.Thus, all potentially nephrotoxic/ototoxic antibacterials) and antifungals – azoles (Itrakonazol, Vorikonazol, Posakonazol) mainly eliminated by liver function are used , while drug-drug interaction could hardly avoidable in such settzings.

TDM is of proven value for minimising toxicity and optimising treatment

3.3. Pain Medications

Most Opioids are metabolised by polymorphic CYP2D6, while among patients ultra rapid metabolisers (UM), extensive metabolisers (EM), intermediate metabolisers (IM)

Poor metabolisers (PM) about .5-10% Caucasians, 1-4% other ethnic groups exist.

Differences in drug metabolism can lead to severe toxicity or therapeutic failure by altering the relationship between Css blood concentration and dose. Many pain patients are co-prescribed other

drugs – large scope for drug/drug interactions. ThereforeTDM may be of value for minimising toxicity and optimising treatment under certain circumstances.Although the current evidence is insufficient to mandate TDM in routine practice, a concerted investigation should be encouraged to determine whether the steady-state trough measurements of targeted agents will have a practical place in the clinical care of patients with cancer.Genetically determined causes of cellular resistance undoubtedly contribute to effective resistance of human tumors,but they represent only one contributing mechanism.,whereas the causes of drug resistance of human solid tumors are multifactorial.There is some evidence for a mechanism that may also have a profound effect on the outcome of chemotherapy—the limited penetration of anticancer drugs through tissue pertaining to pharmacokinetics and pharmacodynamics Even a drug to which the constituent tumor cells are highly sensitive will have limited efficacy if it only reaches some of the target tumor cells in low concentration.[34]Therapeutic drug monitoring (TDM) and more recently target concentration intervention (TCI) have been widely used in clinical practice for the optimization of drug treatment. TDM and TCI have been applied most frequently in the cardiovascular, respiratory, neurology, and infectious disease areas because the medications used here have both narrow therapeutic indices and a clear relationship between concentration and effect. However, apart from drugs such as methotrexate and 5-fluorouracil, the clinical application of TDM/TCI in oncology is minimal. An important reason for this is that a therapeutic index for most anticancer agents has not been established. However, in the last 20 years, relationships between plasma drug concentrations and clinical outcome have been defined for various chemotherapeutic agents. Defining concentration-effect relationships is also complicated by the fact that cancer is almost always treated with multiple drugs given in combination making the precise definition of the pharmacodynamics of individual agents difficult. The increase in patients with obesity and also those underweight adds to the complexity of effective oncology treatment. This review describes some of the evidence that supports the use of TDM/TCI in oncology. It is proposed that as more patients previously ineligible for chemotherapy become eligible, TDM/TCI may play a critical role in optimizing chemotherapy outcomes. However, pharmacokinetic-pharmacodynamic research to investigate both therapeutic benefit and feasibility in daily clinical practice is required.[35] It is well known that efficacy and toxicity of anticancer agents are highly variable between patients and variation in drug disposition is thought to be an important determinant, where Genetics is among underlying factors contributing to this variation. Phenotyping drug metabolizing enzymes and drug transporters by using in vivo probes is also a method that can be used to individualize drug therapy.[36] Very promising recent advances in nanotechnology for treating cancer which address some of the challenges and opportunities in the field is promising [37],for example , Targeted drug delivery, sometimes called smart drug delivery [38], is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. This means of delivery is largely founded on nanomedicine, which plans to employ nanoparticle-mediated drug delivery in order to combat the downfalls of conventional drug delivery. These nanoparticles would be loaded with drugs and targeted to specific parts of the body where there is solely pathologically affected tissue, thereby avoiding interaction with healthy tissue.However, the utilization of new advances may take far longer research so that therapeutic monitoring of the conventional tdrugs is inevitable.

4. Conclusions

Unfortunately We may not completely eliminate adverse effects of chemotherapeutic intervention. However, We can at least minimize adverse effects so that we may reasure the benefit overweighes the possible harm following key steps:

1. Know your patient exellently

2. Make the right (accurate)diagnosis and complex evaluation of the condition, choose the best alternative among all possible taking in account the existing limitations.

3. Apply therapeutic drug monitoring whenever relevant to pharmacokinetic/pharmacodynamic principles.

4. Be always awre of drug-drug, drug-disease interactions in individua patients.

5. Do not drug treat every symptom at the expense of duality of life and overall outcomes.

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