The Current Status and Future Prospects of Therapeutic Drug Monitoring of Chemotherapy in Jordan

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ABSTRACT

In the last 20 years, several prospective studies have been conducted to improve the expediencyof Therapeutic Drug Monitoring(TDM) application in the field of oncology. However, to start and maintain modern TDM services in developing countries requires more funding and education to reform clinical practices.In the present study, we aimed to determine the current practice of chemotherapy and non-chemotherapy TDM in Jordan.A self-administered questionnaire was developed based on reviews of current state-of-art technology and knowledge with respect to TDM of chemotherapeutic and non-chemotherapeutic agents that are frequently used in oncology. The survey was conducted between December 2009 and February 2010 in two main cancer centers in Jordan. Initial dose individualization based on BSA (96.8%) was indicated as the most common approach. Only 17.5% (n=7) and 67.7% (n=27) of the participants indicated that TDM services are routinely provided forchemotherapeutic or non-chemotherapeutic drugs in cancer patients at their institutions, respectively. The most frequent chemotherapy TDM requests were for methotrexate (n=5) and 5-fluorouracil (n=3), whereas most non-chemotherapy drug level determinations were for tacrolimus (n=22) and cyclosporine (n=22). The majority (83.9%) of respondents acknowledged the unavailability of specialized software for dose adjustment based on computer modeling of observed serum levels.Herein, the evidence presented in this study of low rates for drug concentration monitoring in cancer patients should prompt additional awareness programs of TDM clinical and appropriate economic outcomes, particularly for certain therapeutic regimens of proven value.

Keywords: Therapeutic drug monitoring (TDM), chemotherapy, multidisciplinary, professional training, Jordan.

INTRODUCTION

Of the many issues now confronting medical professionals, none seems more important than the debate about enhancing the quality of care.[1,2] Multidisciplinary quality improvement efforts are playing an increasing large role in medical care.[3] Hospitals are trying to improve quality through developing multidisciplinary quality improvement projects.[4]

Therapeutic Drug Monitoring (TDM), the measurement of drug concentration in blood, is employed to estimate blood drug levels so that the most effective dosage can be determined and toxicity prevented.[5]In terms of the quality assurance, it has been shown that development of TDM services can improve the quality of patient care.[6,7]

Although it is known that new methods and technologies carry in themselves extra costs, it is anticipated that growing expertise in TDM will improve its cost-benefit ratio. Despite the potential increase in acquisition cost,several pharmacoeconomic studies have documented the positive impact of TDMand clinical pharmacokinetic services on a patient's outcome. As a result, toxicity may be reduced and achievement of the maximum effect is obtained in the shortest possible time. Furthermore, the duration of a hospital stay could be reducedand, most importantly, lower mortality trends

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may be achieved.[8,9]

Moreover, TDM has been highlighted as a unique clinical discipline that combines the determination of drug levels with the application of pharmacokinetic principles and pharmacodynamics to optimize dosage regimens in a patient.[5]Therefore, therapeutic drug monitoring services are deemed to have a greater role than mere therapeutic drug measuring.[7]According to this distinct definition of TDM, a number of complementary specialties should be employed to produce high quality services and optimum health outcomes. Thus, the ideal TDM team should include clinical pharmacologists, clinical pharmacists, nurses, phlebotomists, clinical chemists, toxicologists, analytical chemists and physicians.[10,11]Each person in the team should be assigned tasks involved in a sequential process, including correct administration of the drug, correct collection and processing of blood samples, precise and accurate estimation of the drug, and finally, appropriate interpretation of the results.[10,12] In actual practice, this multidisciplinary field has mainly been set-up within teaching hospitals and to a lesser extent in the private sector.[13]Moreover, different levels of TDM services can be identified depending on international or local strategies and monitoring protocols that have been developed; these strategies and monitoring protocols may be used to modify doses of certain therapeutic areas, depending on the available resources, laboratory techniques, computer programs, and team's skills in pharmacokinetics.[6]

To date, in many countries worldwide, TDM has been applied in routine practice with mainly 'traditional' drugs that have narrow therapeutic ranges or may induce severe toxicity. In particular, more frequent TDM requests have been reported for drugs which have simple immunoassays such as aminoglycosides, vancomycin, digoxin, theophylline, and anticonvulsant.[11,14]Moreover, motivating developments in TDM of extensively metabolized drugs such as immunosuppressants, antiretroviral therapy and psychotropic drugs are still advancing. However, further research evaluations are considering incorporating TDM into the routine care to aid doctors' decisions in dosage adjustments of these drugs. Generally, in such therapeutic areas, high intra/interindividual variability in pharmacokinetic parameters was found. Therefore, dosage requirements are anticipated to be significantly unpredictable, particularly with respect to genetic and ethnic factors.[15-17]

TDM of Cancer Chemotherapy

Since the 1950s, the chemotherapeutic agents have been traditionally individualized based on body surface area (BSA in mg/m^2). However, this method is often imprecise due to considerable variability in tumor heterogeneity[18]and patient genetic composition, as well as unpredictable changes in pharmacokinetic and physiological status of various patient subgroups.[19]Therefore, further non-BSA- dosing methods[19-21]were derived and mostly classified into three categories: (i) the *a priori* methods, which allow the estimation of the dose required to achieve the target exposure in certain patient variables that may affect drug concentration profiles, such as body weight, age, gender, serum creatinine level, and glomerular filtration rate; (ii) the test dose method, which involves a collection of multiple blood samples after administration of a bolus injection of a low or a small dose, followed by a readjustment of the dosage based on newly calculated individual pharmacokinetic parameters for each patient; (iii) the *a posteriori* methods, which require both concentration data and sometimes additional physiological or biological factors known to account for pharmacokinetic variability. While the first method category is based on general guidelines and does not comprise any drug concentration (non-TDM method), these guidelines are frequently indistinct and empirical. Therefore, more serum concentrationor TDM-based dosage individualization methods such as those included in third category(the use of nomograms, multi-linear regression or Bayesian estimation) have been more commonly suggested. Hence, in the last 20 years, several prospective studies have been conducted to improve the practicality of the TDM application in the field of oncology due to its proven benefits for controlling toxicity and improving efficacy of certain

chemotherapeutic agents including carboplatin, methotrexate, 5-fluorouracil, etoposide, busulfanand 6-mercaptopurine.[19-21] Yet the TDM process in oncology is deemed quite more complex than other therapeutic areas. This has hindered its routine clinical practice[19,20], mainly due to the existence of a long lag period between the measurement of drug concentration in plasma and the evaluation of long-term clinical outcomes which include tumor response survival rate, toxicity or even death. Secondly, there is some difficulty in determining the concentration-effect relationship for a single drug since antineoplastic agents are mostly used in combination. Thirdly, tumor heterogeneity may alter drug systemic exposure requirements, due to variability in cellular resistance, blood supply and tumor kinetics according to various cancer types.[19] Other logistical limitations include the requirement of a strict adherence to multiple sampling schedules over a period of time during and after drug administration for many dosage individualization methods, as formerly discussed. This may delay the beneficial effects for the patient and may not always be feasible in clinical practice. However, these difficulties can be resolved by the implementation of more flexible dose adaptation methods, which require few sampling points such as nomograms, limited sampling strategy or more accurately providing PK estimates by Bayesian adaptive-control strategies.[21] Nevertheless, the latter methods demand an institution to provide their TDM unit with a computer (with user-unfriendly software). Clinical pharmacists who are well-trained in advanced techniques for PK-modelling[21,22] are also required to perform initial dosage calculations and further adjustments for anticancer, as well as non-anticancer drugs in cancer patients.[23] Another crucial requirement for implementing TDM in daily practice is the accessibility of robust, fast and reproducible analytical methods for determining drug levels; this can be more practical and less laborious than high-performance liquid or gas chromatography-based methods. Perhaps in this context, more specialized cancer institutions can provide consultations to other generalized hospitals and clinics.

Moreover, to start and maintain a modern TDM service in developing countries more substantial funding and implementation efforts are required. Education endeavors are also necessary to change clinicians' behaviors and convince them to amend their practices. In fact, though this type of service has not been well-established in Jordan, there is no estimate available regarding the actualadoption of TDM by other health care systems and its application in hospitalsaround the globe. Given this background, in the present study, it is aimed to determine the situation inJordan regarding non-cancer drug measurements. In addition, the investigation of the current practice of chemotherapy TDM is also described.

Methods

A self-administered questionnaire was developed based on reviews of the current state-of-art technology and knowledge with respect to TDM chemotherapeutic and non-chemotherapeutic agents that are widely used in oncology.[18-23] No other questionnaire as such was located from previously existing literature, so a specific questionnaire had to be designed to achieve the aims of this study. The initial questionnaire was piloted among 10 clinical pharmacists who attended a prearranged TDM workshop; the participants worked in public hospitals and were also based within academic universities. All comments were included in the final version of the questionnaire.

The questionnaire was distributed as a hard copy from December 2009 to February 2010 among 100 staff members in two main cancer centers in Jordan. The survey forms were given to pharmacists, clinical pharmacists, analytical chemists and resident physicians through individual visits to hospitals. They were either completed immediately, collected at a later date or mailed back to the researchers. Members were informed about the purpose of the survey, anonymity was assured and participation was voluntary.

The questionnaire comprised 17 questionswith two types of response: afree-text response or a pre-defined checklist. However, in both types the respondents were given the option to answer "I don't know" in order to reduce inaccurate responses and guessing. The questionnaire form consisted of four sections: initial

dosing strategies, monitoring activities, subsequent (posteriori) dosing guidance and future prospects of TDM services.

The first section asked about the various drugs included in the institutions' chemotherapy protocols. It also asked about their strategies for dose individualization, and whether this was done according to any standard guidelines or patient factors such as BSA, age, weight, etc. The second part of the questionnaire included inquiries regarding the nomination of chemotherapy and non-chemotherapy drugs being routinely monitored and their frequency of monitoring (number of drug level requests per case or per week). Participants were also asked to select other alternative or concurrent clinical parameters that were used to assess the efficacy and safety of these drugs. For questions concerned with target concentration policies for each drug, sampling strategy (e.g. peak, trough, average of steady state, etc.) and the type of assay technique provided in the internal or external labs, participants were requested to enter their own answers.

The third part of the questionnaire inquired about the availability of dosing guidance software, program names, whether Bayesian forecasting was routinelyused, and other posteriori dose individualization techniques based on patient's measured serum concentration. Additionally, participants were asked to identify members who are mostly involved in the dosing adjustment or interpretation of observed concentrations in relation to clinical outcome.

In the final part of the questionnaire, the respondents had the opportunity to rate their knowledge of TDM according to suggested levels of experience. In addition, they were asked to identify other professional training activities and advanced courses they thought would be beneficial to acquire basic principles or improve their knowledge and skills in TDM services. Furthermore, all respondents were asked whether they aspired to be more involved in a TDM service that is concerned in the particulartherapeutic areas that they believed would be more important.

All data were coded, entered and analyzed using the SPSS© software (version 17.0; SPSS, Inc, Chicago, IL). For interested readers, a copy of the final questionnaire can be requested from the author.

Results

Demographic Details of Respondents

Of the 100 questionnaires sent, 40 completed submissions were returned. Therefore, the response rate was 40%. The demographic details of respondents are given in Table 1. Of the respondents, 52.1% were men while 47.9% were women. The average age was 28.5 (±1) years, with the predominant age group between 20-29 years of age, followed by 40-49 years. More than one-third of the respondents (37.5%) were clinical pharmacists, while most of the survey respondents had one to five years of experience in their current institution (mean, 4.43 ± 5.1).

TABLE 1. Demographic Characteristics of Survey Participants (n = 40).

Characteristic	Respondents, (%)
Age group	
20-29 years old	22 (55)
30-39 years old	8 (20)
40-49 years old	10 (25)
Level of Qualification and Specialty	9 (22.5)
Bachelor of Science in Pharmacy	3 (7.5)
Master of Science in Clinical Pharmacy	12 (30)
Doctor of Pharmacy	11 (27.5)
Resident Physician	5 (12.5)
Analytical Chemist	
Years of experience	
< 1	3 (7.5)
1-5	22 (55)
6-10	4 (10)
11-15	3 (7.5)
16-20	6 (15)
21-25	2 (5)

Initial Dosing Strategies

Among the most commonly employed chemotherapeutic agents (Figure 1), methotrexate followed by fluorouracil were the most recurrently nominated drugs in the survey. When the respondents were asked about current knowledge of initial dose individualization *(priori)* methods of the previous drugs (Figure 2), dose estimation based on BSA (96.8%) was indicated to be the most widely existing approach in the participants' institutions. Initial dose individualization according to body weight (74.2%) was the second most highly selected method, with age-adjusted modification (48.4%), standard (flat-fixed) dose (45.2%) and nomograms (25.8%) constituting the remainerof the participants' responses to this query. None of the respondents indicated awareness of any other dose adaptation strategies based on other biological or clinical patient variables.

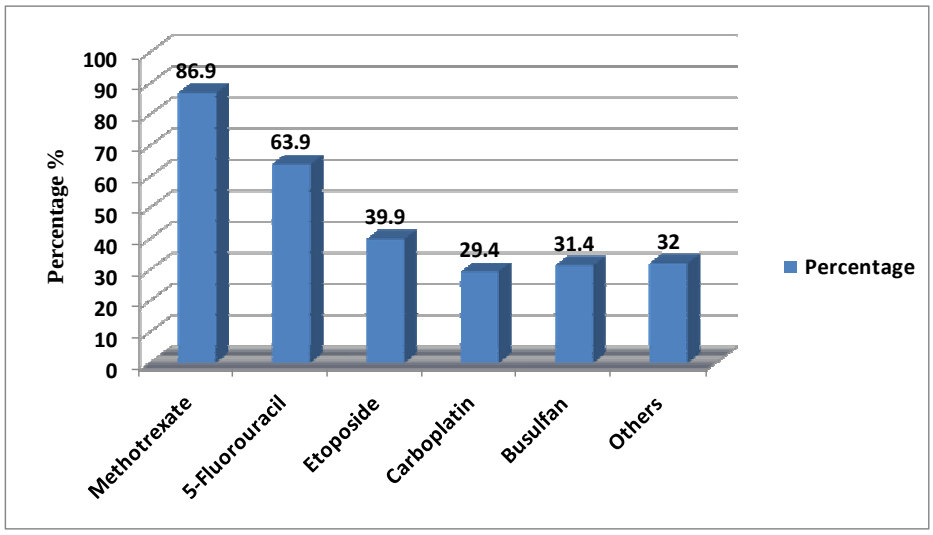

Figure1:The Frequency of Commonly Employed Drugs in Various Chemotherapy Protocols(n=40)

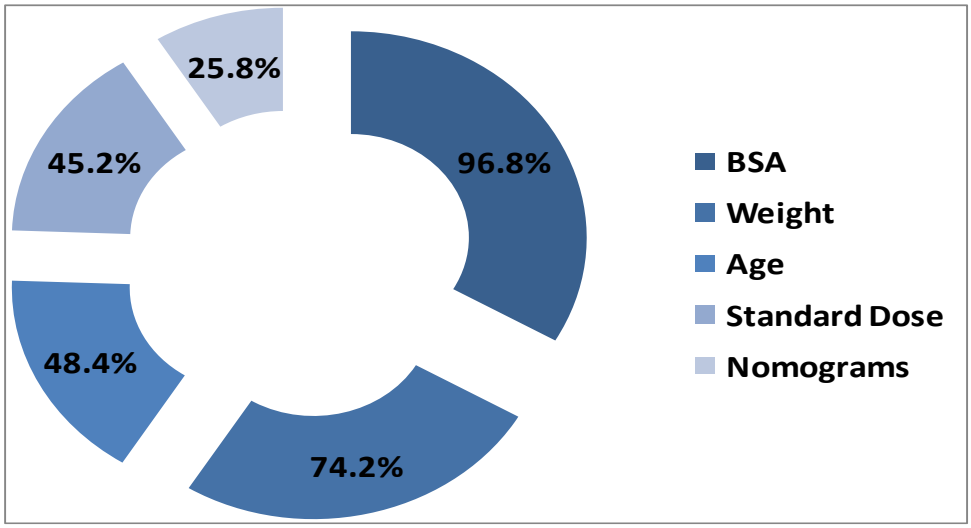

Figure 2:The Frequency of Initial Dosing Strategies (n=40.

Monitoring Activities

Participants were asked whether they routinely monitored plasma levels after the start or change of chemotherapeutic or non-chemotherapeutic drugs in cancer patients. Only 17.5% (n=7) and 67.7% (n=27) of the participants indicated that such monitoring activities and services are provided for these two medication categories, respectively. The majority of respondents stated that such services are not routinely considered, or that they did not know whether routine monitoring was available in their institution.

Monitoring Activity Frequency

For those who responded positively to the previous section (n=27, 67.7%), other details regarding nomination of drugs being routinely monitored and frequency of monitoring (number of drug level requests per case or per week) were obtained. As illustrated in Table 2, their knowledge of commonly employedsampling strategies for each specific drug is also summarized. The most frequent chemotherapy TDM requests were for methotrexate (n=5) and 5-fluorouracil (n=3), whereas most non-chemotherapy drug level determinations were for tacrolimus (n=22) and cyclosporine(n=22). With respect to sampling strategies for the purpose of methotrexate monitoring, respondents recommended obtainment of one sample at the peak (n=1) or at the end of infusion to ensure the achievement of a steady state (n=2), or three samples at specified times during and the end of infusion (n=5). For 5-fluorouracil, the average concentration after 4 days was suggested (n=3). For the other two chemotherapeutic drugs, carboplatin and busulfan, only one participant responded and defined two alternative sampling strategies (Table 2). For other non-chemotherapeutic drugs, the choice of trough sampling was prevalent, except for cyclosporine with more respondents recommending sampling at 2 hours post-dose (20 of 22, 90.9%), and for vancomycin with more trends for peak sampling responses (4 of 4, 100%). In addition, many participants advocated random sampling to rule out suspected toxicity in the case that severe signs and symptoms for tacrolimus, theophylline or digoxin were observed.

Target Concentration Policy

Moreover, participants were asked if there were any defined targeted policies (orranges) as part of their centers' protocols for guiding the assessment of the efficacy and safety of chemotherapy and non-chemotherapy drugs. The percentages of staff members' responses reveal that none of the participating staff members were aware of the availability of such protocols. Almost ninety seven per cent (96.8%) of respondents said that there were no polices in their centers for drug concentration measurements. On the other hand, only 3.2% stated that they were not sure of their answers.

Assay Methods

Of particular note, spectrophotometry (54.8%) followed by high-performance liquid chromatography (HPLC) (38.7%) were the most highly selected methods by participants. In addition, immunoassay and gas chromatography were among the less frequently reported methods.

Subsequent (Posteriori) Dosing Guidance

1. Software for Calculation and Dose Adjustment

Asking about the availability of any software for dose calculation and adjustment based on measured plasma concentrations in individual patient cases, only 23% indicated the availability of such software, but did not specify any program names. A percentageof respondents (6.5%)instead selected "I don't know," indicating their unfamiliarity with this sort of activity in their centers. When asked whether Bayesian forecasting is routinely employed for dosing guidance, only approximately 10% of the participants expressed familiarity with this approach of pharmacokinetic modeling for monitoring drugs using concentration data. However, no participants clearly indicated their routine employment within their practice. With respect to knowledge of other posteriori dose individualization methods among the participants who did not recognize Bayesian technique, most chose calculations based on population PK-parameters (48.4%). Even fewer selected test dose method (38.7%), nomograms (25.8%) or multi-linear regression methods (19.4%). Again, despite acknowledgement of previous

methods, only few (25%) declared, however, rare applications of pharmacokinetic dosage calculations based on available patient variables.

2. Clinical Monitoring

Figure 3 displays the clinical monitoring and laboratory parameters which were thought to be relevant for evaluating the efficacy and safety as well as for subsequentdosage adjustments of chemotherapeutic drugs in conjunction with drug levels during the follow-up. As shown, the leucocyte and platelet nadir were the most highly reported.

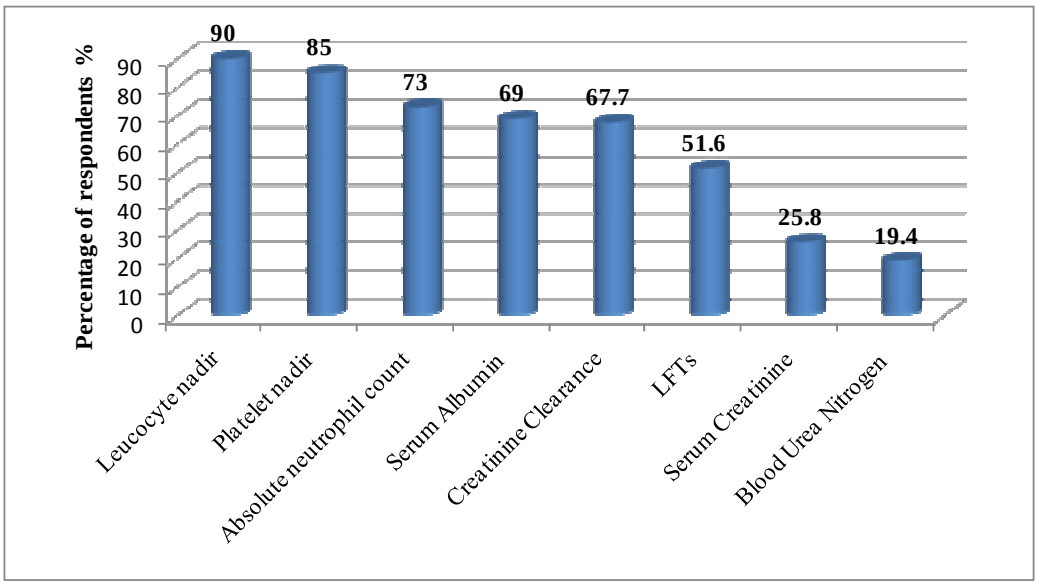

Figure 3: Clinical Monitoring Parameters in Oncology Patients (n=40).

Professions Involved in TDM

When asked to indicate which professions should be involved in the interpretative service of drug concentrations with or without pharmacokinetic consultation, the most frequently cited profession was physicians (77.4%) followed by clinical pharmacologists (71%). Surprisingly, pharmacistswere less frequently nominated (58.1%). A small percentage of the respondents (6.5%) felt that clinical chemists could present valuable advice,especially with regard to the interpretation of the measured drug concentration values.

Future Prospects of TDM Services

Perceived and Actual Knowledge in TDM

When respondents in the two cancer centers were asked to rate their extent of knowledge in this area of science, 42.5% felt their perceived education was very good, 25% believed that they had satisfactory knowledge and 25% affirmed their poor knowledge of this topic. Only 7.5% of participants felt they knew a great deal about this issue, having sufficient practical experience and application.

Interest In and Need for Additional PK-Courses

The majority of respondents (77.4%) declared their need for additional basic or advanced PK courses to review or acquire basic knowledge they thought they did not have in their curriculum. The frequency of nominated courses was as follows: Applied Pharmacodynamics (64.5%), Advanced Clinical PK (45.2%), Applied Clinical PK (41.9%) and Basic Concepts of PK (19.4%).

Sources of Professional Training

In addition, all staff surveyed pointed out the significance of professional training to provide sufficient skills to gain competency in the field of TDM service. A

large percentage (87%) of the respondents indicated that they believed that this would be greatly appreciated by their employers. With regard to the inquiry about the sources of professional training and skills in TDM, participants were most interested in pursuing continuing education courses (80.6%) and attending TDM workshops (77.4%). Interestingly, a significant percentage of surveyed staff (41.9%) was keen to participate in research activities related to TDM issues.

TDM of Other Therapeutic Areas

Out of four listed TDM subspecialties, 40% of staff expressed an interest in the area of tricyclic antidepressants, 32% displayed more concerns about immunosuppressive agents and 21 % put a high significance on antiretroviral drugs employed in the treatment of AIDS. Yet, fewer participants (7%) regarded TDM in the management of patients with tuberculosis (TB) as a useful tool in the setting of multidrug-resistant TB.

Discussion

Initially, the findings of this study provide basic information to guide the establishment of good standard TDM services in Jordanian health institutions. In the global picture, the current audit was sought to foster the clinical staff education and orientation towards rational drug concentration measurement and interpretation, with special emphasis on a cancer patient setting.

The routine TDM applications have been mainly reported for drugs described as toxic or as causing severe side effects in the literature—though to a variable extent of sophistication by different institutions throughout the world. Well-known "traditional" examples are antiepileptic drugs, antiarrhythmic agents, theophylline, aminoglycoside antibiotics, cardiac glycosides and drugs to prevent transplant rejection.[14-17] TDM has also been utilized to identify noncompliant patients, regardless of the drug indicated for them.[24]

However, despite proven and expected beneficial impacts of TDM in cancer patients, in terms of improving efficacy, controlling toxicity and reducing drug-drug interactions, its application remains limited and confined to certain chemotherapeutic agents.[19-21]This gap between research and clinical practice was attributed to several factors, mainly, due to poorly defined concentration- and/or exposure-effect relationships for many antineoplastic agents.[20] However, it was agreed that treating physicians still ought to consider variability in patient age, disease stage, multiple comedication,tumor heterogeneity and degree of organ function in tailoring dosage regimen for an individual cancer patient.[23] In fact, with further accumulating evidence from many new PK studies for various chemotherapeutic agents and with recent advancements in computer modeling techniques, the application of TDM in routine oncology clinical practice is becoming more feasible. Therefore, any previous difficulties should no longer hinder its adoption in cancer institutions worldwide.

According to the main Jordanian cancer institutions, this pilot study's data revealed a lack of knowledge about modern initial dose estimation methods of chemotherapeutics among the majority of clinical staff. A majority (96.8%) of the participants citedBSA as the sole parameter on which to base dose calculation. This was deemed to be inaccurate to standardize the apparent interpatient variation in PK for most cytotoxic drugs.[18]Consequently, continual use of a fixed dose based on a BSA calculation might lead to life-threatening side effects in certain patients, or result in the treatment failure for others.

With regard to monitoring activity, in this study, it was defined by the frequency of requesting a drug level for a chemotherapeutic drug per week or per case. Unpredictably, this activity was very rare (2.5% to 17.5%) or almost absent (0%) for most of the employed chemotherapeutic agents covered in the current survey. Interestingly, methotrexate was the most frequently ordered assay, constituting 70% of all chemotherapeutic drug tests as stated by our respondents (5 of 7). Perhaps this finding can be explained by the availability of easily applicable commercial immunoassay for methotrexate serum determinations, while only more expensive and difficult separative methods are found for other drugs.[24,25] Alternately, another possible explanation is the previously reported evidence of valid clinical impact of

its level routine use by highly specialized centers for individual dose adjustments of folinic acid as an antidote.[26]Another chemotherapeutic agent, which was less frequently measured as mentioned by our surveyed staff, was fluorouracil (3 of 7). This again can be attributed to the recent introduction of simple, fast and inexpensive testing methods based on a liquid chromatography-tandem mass spectrometry and a nanoparticle antibody-based immunoassay which may facilitate its routine monitoring in daily clinical practice.[27]Additionally, since its systemic exposure has been significantly correlated withthe risk of toxicity and treatment efficacy, TDM for fluorouracil may be useful.[28]

From a practical point of view, examining the accuracy, precision, sensitivity and specificity of each assay of drug concentration is a mandatory initial step to support a comprehensive and reliable TDM service.[7,21]This preference can also be clinically supported by setting a target concentration policy or therapeutic window for estimated drugs, according to specific patient conditions. In this context, the lack of unified concentration policies for chemotherapeutic agents reported in the current survey (96.8%) was considered misleading, particularly in light of the numerous published studies demonstrating a clear relationship between the extent of systemic exposure (AUC or C_{SS}) and toxicity or efficacy for many cytotoxic drugsincluding methotrexate[29], etoposide[30], carboplatin[31], fluorouracil[28], topotecan[32] and Busulfan[33].

Moreover, cancer patients are more prone to have drug-drug interactions due to the regular indication of various wide spectrums of non-anticancer drugs, including antibiotics, antifungal agents, digitalis, immunosuppressants and anticonvulsants.[23]This factor of multiple comedications would definitely affect the chemotherapeutic drug levels, leading to a non-optimal exposure with a subsequent potential for therapeutic failure or toxicity. Therefore, it was suggested that TDM of non-anticancer drugs within oncology would be more pressing.[23] According to the current survey, the reported monitoring frequencies were scarce and only limited to a number of'traditional' drugs for which immunoassays are internally available, including immunosuppressants, theophylline, digoxin, carbamazepine, vancomycin and amikacin. Based on our current preliminary observation, the overall data suggests that many drugs are being poorly monitored in comparison with the findings of past international studies[34-36] and that further awareness programs are warranted among staff to achieve a more effective TDM for non-chemotherapeutic drugs as well. However, it is essential to develop international best practice guidelines that allow the accurate assessment of all aspects of TDM.[36]In the absence of such guidelines, it seems unfeasible to estimate the gap of any of these drugs' TDM in Jordan as compared with internationally accepted standards.

For a TDM result to be appropriately interpreted, the sampling time with respect to the last dose should be properly defined.[7,37]Additionally, a clinician's lack of knowledge about TDM procedures may lead to an inappropriate time of collection and inaccurate documentation of the time of drug administration and serum concentrations, thus necessitating retesting and increased costs.[38]Based on our data, it appears that the knowledge of our participants regarding sampling time wasscant as a few number of responses (2 to 22 respondents) were received for most drugs being monitored (Table 2).Tacrolimus trough was the most remarkable indicated response, despite its questionable correlation with efficacy outcomes.[39]Once again, this highlights the need for further literature review and/or consensus guideline consultations to select proper sampling times.

With respect to posteriori dose adaptation methods, several studies have illustrated that anticancer treatments can be successfully optimized by using more sophisticated and more precise dose individualization methods based on prospective drug concentration in each patient with an adjustment for the body's surface area.[19-21] Moreover, Bayesian forecasting and estimators have been used with encouraging results in terms of toxicity control; this is due to more accurate dose and administration schedule adjustments for both chemotherapeutic[26,40] and non-chemotherapeutic agents.[41]

Yet, very few of our participants (approximately 10%) declared their awareness of the pharmacokinetic modeling approach for assisting in the analysis, interpretation and further monitoring of drugs using concentration data. This finding was further explained when a high percentage of staff expressed their needs for additional courses in PK (77.4%) and further professional training (80.6%) in employment of PK-modeling computer software programs.

However, as an alternative to PK-parameters, it appeared that the majority of participants are aware of several laboratory measurements employed for the evaluation of side effects, and particularly hematological toxicity induced by chemotherapy due to severe myelosuppression. This is possibly because the latter tests are easily obtained and can serve as helpful early indicators for decreasing the dose. However, these tests are not predictors for efficacy and are not unique to one drug.[19]Therefore, we can not rely on such endpoints as the solitary therapeutic targets.

Previous reports have established that a TDM process involves a number of sequential steps which require the skills and knowledge of various professionals (pharmacists, clinical pharmacologists, nurses, clinical chemists and physicians).[7,12] Hence, in order to fully optimize its application in a clinical setting, all members of a TDM should collaborate and communicate various pieces of information in order to better control and monitor the whole process.[18] However, this concept of multidisciplinary effort appeared unfamiliar to our respondents, and most nominated physicians as the solely involved profession (77.4%). Pharmacists were less frequently designated (58.1%). These results suggested that several other professionals in the survey were not well aware of pharmacists' work in relation to TDM.

In terms of future prospects, all of the participants displayed enthusiasm in exploring various medical fields in which TDM is likely to be of benefit. Yet it is obvious that implementing such a service in a developing country would initially be costly. Such cost is not only related to the expenses of multiple drug assays, but also to the increased duration of hospitalization and time consumed by additional staff members to monitor and interpret. Therefore, it would be more promising if the Jordanian cancer treatment centers became involved in the international prospective multi-center TDM studies. This could also be valuable in terms of gaining more experience and insight into good standards of the TDM process.

Although the results of this study are interesting, there are several important limitations that should be considered when interpreting the data. First, the study was performed at a single site (Amman; the capital city of Jordan) and within medical centers mainly providing care for cancer patients. Therefore, the results may not be representative of other health care professionals who work in urban areas outside of Amman or even those working in non-cancer medical fields inJordan.

Additionally, the design of the study was of a cross-sectional design which examined the knowledge and status of TDM services within that period of time. Yet, it would be more interesting to repeat it after a period of time has elapsed or to follow up the same population for a longer time to reexamine their responses after implementing some intervention such as pursuing continuing education courses, attending TDM workshops or participating in research activities related to TDM issues. Also, although the study involved participants with different specialties, educational background and qualification levels, responses'rates were not stratified according to these variables due to the small sample size in small subgroups. This may have influenced the currently obtained high rate of negative response to some questionnaire items due to lack of knowledge. This issue can only be confirmed by further segregation of responses according to specialty, but in a larger study. Finally, due to all previous limitations we acknowledge that the theme of TDM application and knowledge merits further large-scale investigation of the healthcare population perspectives and awareness about its clinical and economic benefits in parallel with the further evaluation of the impact of this survey on increasing awareness of members who may play the most crucial task in this service such asclinical pharmacists.

Conclusion

The advanced ongoing investigations around the globe are refining the definition of PK/PD relationships and validating the TDM of oncology in terms of developing modern methods for the measurement of drug concentrations, evaluating clinical effects as well as for data processing. Nevertheless, the Jordanian expertise in this area still lags behind and further intensive education and awareness programs should be initiated.

Moreover, the insight provided by this study indicated that the TDM process in Jordan concerning other traditional drugs in the non-chemotherapy area is still far from the lowest standards available elsewhere and has many challenges ahead. Wise, well-funded application is encouraged in order to optimally enhance care and improve the cost-benefit ratio. Enhanced knowledge of PK/PD modeling,particularly with the use of specific software, is required among senior and junior clinical pharmacists.

It is also hoped that more multidisciplinary professions will become committed to future TDM needs so that the TDM practice in Jordan can transform into a widespread reality.

Impact of Findings and Recommendations

- The results of this study demonstrate areas in the chemotherapy TDM process where further education and awareness efforts should be initiated to achieve better standards and desired clinical outcomes. These mainly include initial dosing methods, posteriori dosage individualization based on drug concentration and PK-modeling, timing and number of sampling, frequency of monitoring of non-anticancer drugs in cancer patients and the interpretation of measurements within target concentration policies.
- The results of this study provide information to guide the thoughtful establishment of quality-of-care indicators related to TDM in the oncology area.
- The low rates of non-cancer drug concentration monitoring evidence presented in this study should prompt the establishment of additional awareness programs for TDM clinical and economic outcomes, particularly for certain therapeutic regimens of proven value.

The extent of knowledge expressed in this study emphasized that it is of great importance that health professionals are kept well-informed about the latest developments concerning TDM.

Table 2:The Frequency of Drug Level Requests and Sampling Strategy for Chemotherapy and Non-Chemotherapy in Cancer Patients*

Drug (No. Respondents)	*Frequency/week*	*Frequency/case*[§]	*Sampling Strategy*			
			Trough	*Peak*	C_{ss}	*others*
Chemotherapy (n=7, 17.5%)						
Methotrexate (n=5)	1	2		1	2 (end of infusion)	5 (1 and 6 h after start first 24-h infusion, then at 48 h)
5-Fluorouracil (n=3)	1	2			3 (4 days)	
Carboplatin (n=1)	1	2				1 (1 and 4 h after end of infusion)
Busulfan (n=1)	1	3			1 (5^{th} dose)	1 (5 samples for AUC)
Non-chemotherapy (n=27, 67.7%)						
Tacrolimus (n=22)	2	10	22			10 (random if toxicity suspected)
Cyclosporin (n=22)	2	12	2		4	20 (C_2, 2 h after dose)
Theophylline (n=19)	1	2	12		7	19 (random if toxicity suspected)

Drug (No. Respondents)	***Frequency/week***	***Frequency/case§***	***Sampling Strategy***			
			Trough	***Peak***	***C_{SS}***	*others*
Digoxin (12)	1	1	12		12	7 (random if toxicity suspected)
Carbamazepine (n=7)	1	2	7	7	7	
Vancomycin (n=4)	1	1	3	4		
Amikacin (n=2)	1	1	2	2		

*Total participants responding to this question (n=27); §, average frequency per case during hospital admission; C_{SS}, Steady state average concentration; AUC, area under the plasma concentration-time curve.

REFERENCES

(1) Umbdenstock R. Next steps. Push ahead on quality and safety efforts. Mod Healthc 2010; 40 (13): 25.

(2) Jonna JH. Enhancing quality oversight. Study findings show hospital boards increasingly focused on quality initiatives. Healthc Exec 2010; 25 (2): 80, 82-83.

(3) Lobdell KW, Stamou SC, Mishra AK, et al. Multidisciplinary rounds: the work, not more work. Ann ThoracSurg 2010; 89 (3): 1010.

(4) Blobel B. Architectural approach to eHealth for enabling paradigm changes in health. Methods Inf Med 2010; 49 (2): 123-134.

(5) Watson I, Potter J, Yatscoff R, et al. Editorial. Ther Drug Monit 1997; 19 (2): 125.

(6) Shenfield GM. Therapeutic drug monitoring beyond 2000. Br J ClinPharmacol 2001; 52: 3S-4S.

(7) Gross AS. Best practice in therapeutic drug monitoring. Br J ClinPharmacol 2001; 52: 5S-10S.

(8) Tonkin AL, Bochner F. Therapeutic drug monitoring and patient outcome.***ClinPharmacokinet***1994;27:169-174.

(9) Touw DJ, Neef C, Thomson AH, et al. Cost-effectiveness of therapeutic drug monitoring: a systematic review. Ther Drug Monit. 2005; 27(1):10-17.

(10) Reynolds DJM, Aronson JK. Making the most of plasma drug concentration measurements. Br Med J 1993; 306: 48-51.

(11) Gogtay NJ, Kshirsagar NA, Dalvi SS. Therapeutic drug monitoring in a developing country: an overview. Br J ClinPharmacol 2001; 52: 103S-108S.

(12) Hon YY, Evans WE. Making TDM work to optimize cancer chemotherapy: a multidisciplinary team approach. ClinChem 1998; 44 (2): 388-400.

(13) Wu LW. International Association of Therapeutic Drug Monitoring And Clinical Toxicology: Newsletter. TDM in China. Ther Drug Monit 1996; 18 (3): 319-320.

(14) Eadie MJ. Therapeutic drug monitoring – antiepileptic drugs. Br J ClinPharmacol 2001; 52: 11S-20S.

(15) Cattaneo D, Perico N, Remuzzi G. From pharmacokinetics to pharmacogenomics: a new approach to tailor immunosuppressive therapy. Am J Transplant 2004; 4 (3): 299-310.

(16) Boffito M, Acosta E, Burger D, et al. Current status and future prospects of therapeutic drug monitoring and applied pharmacology in antiretroviral therapy. AntivirTher 2005; 10 (3): 375-392.

(17) Bengtsson F. Therapeutic Drug Monitoring of Psychotropic Drugs: TDM "Nouveau". Ther Drug Monit 2004; 26 (2): 145-151.

(18) Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. J ClinOncol 1996; 14 (9): 2590-2611.

(19) de Jonge ME, Huitema ADR, Schellens JHM, et al.Individualised Cancer Chemotherapy:Strategies and Performance ofProspective Studies on TherapeuticDrug Monitoring withDose Adaptation: A Review. ClinPharmacokinet 2005; 44 (2): 147-173.

(20) Alnaim L. Therapeutic drug monitoring of cancer chemotherapy. J Oncol Pharm Practice 2007; 13: 207–221.

(21) Rousseau A, Marquet P. Application of pharmacokinetic modeling to the routine therapeutic drug monitoring of anticancer drugs. FundamClinPharmacol 2002; 16(4):253-262.

(22) BuffingtonDE, Lampasona V, Chandler MH. Computers in pharmacokinetics. Choosing software for clinical decision making.ClinPharmacokinet 1993; 25 (3): 205-216.

(23) Joerger M, Schellens JH,Beijnen JH. Therapeutic drug monitoring of non-anticancer drugs in cancer patients. Methods Find ExpClinPharmacol 2004; 26 (7): 531-545.

(24) Jaime-Pérez JC, Gómez-Almaguer D, Sandoval-González A, et al. Random serum methotrexate determinations for assessing compliance withmaintenance therapy for childhood acute lymphoblastic leukemia.Leuk Lymphoma 2009; 50(11):1843-1847.

(25) Evans WE, Relling MV, Rodman JH, et al. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukaemia. N Engl J Med 1998; 338: 499-505.

(26) Odoul F, Le Guellec C, Lamagnere JP, et al. Prediction of methotrexate elimination after high dose infusion in children with acute lymphoblastic leukaemia using a population pharmacokinetic approach. FundamClinPharmacol 1999; 13: 595-604.

(27) Breda M, Barattè S. A review of analytical methods for the determination of 5-fluorouracil in biological matrices. Anal BioanalChem 2010;397 (3):1191-1201.

(28) Gamelin E, Boisdron-Celle M. Dose monitoring of 5-fluorouracil in patients with colorectal or head and neck cancer: Status of the art. Clin Rev OncolHematol 1999; 30 (1): 71-79.

(29) Delepine N, Delepine G, Jasmin C, et al.Importance of age and methotrexate dosage: prognosis in children and young adults with high grade osteosarcomas. Biomed Pharmacother 1988; 42: 257-262.

(30) Joel S, O'Byrne Penson K, Papamichael R, et al. A randomised concentration-controlled comparison of standard (5-day) vs. prolonged (15 day) infusions of etoposide phosphate in small-cell lung cancer. Ann Oncol 1998; 11: 1205-1211.

(31) Jodrell DI, Egorin MJ, Canetta RM, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J ClinOncol 1992; 10: 520-528.

(32) Montazeri A, Culine S, Laguerre B, et al. Individual adaptive dosing of topotecan in ovarian cancer. Clin Cancer Res 2002; 8 (2): 394-399.

(33) McCune JS, Gibbs JP, Slattery JT. Plasma concentration monitoring of busulphan: does it improve clinical outcome? ClinPharmacokinet 2000; 39 (2): 155-165.

(34) Manolopoulos VG, ArvanitidisKI.Therapeutic Drug Monitoring and Toxicological Drug Measurement in Greece. Ther Drug Monit 2005; 27(2): 234.

(35) Kshirsagar NA, GogtayNJ, Dalvi SS. Therapeutic Drug Monitoring Services in DevelopingCountry.Ther Drug Monit 1999; 21 (4): 429.

(36) Norris RL, Martin JH, Thompson E, et al. Current status of Therapeutic drug monitoring in Australia and New Zealand: A need for improved assay evaluation, best practice guidelines, and professional development. Ther Drug Monit 2010; 32 (5): 615-623.

(37) Carroll DJ, Austin GE, Stajich GV, et al. Effect of education on the appropriateness of serum drug concentration determination. Ther Drug Monit 1992; 14 (1): 81-84.

(38) Li J, Burzynski JN, Lee YN, et al. Use of therapeutic drug monitoring for multidrug-resistant tuberculosis patients. Chest 2004; 126: 1770-1776.

(39) Wallemacq P, Armstrong VW, Brunet M, et al.Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. Ther Drug Monit 2009; 31 (2): 139-152.

(40) Guillet P, Monjanel S, Nicoara A, et al. A Bayesian dosing method for carboplatin given by continuous infusion for 120h. Cancer ChemotherPharmacol 1997; 40: 143-149.

(41) Proost JH, Meijer DKF. Mw/Pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. ComputBiol Med 1992; 22 (3): 155-163

تقييم النظام الحالي والخطط المستقبلية لمراقبة العلاج الدوائي السرطاني في الأردن

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ملخـص

أجري على مدى العشرين عاماً الماضية عدد من دراسات المتابعة المستقبلية لتحسين الخبرة في تطبيق نظام مراقبة العلاج الدوائي في حقل السرطان، ولكن تأسيس وتطوير هذا النظام الحديث من المراقبة الدوائية السريرية في الدول الناشئة قد يحتاج إلى دعم أكثر من الموارد المالية والتعليمية بهدف تحديث الممارسة السريرية العملية هدفت الدراسة الحالية لوصف الممارسة الحالية المتبعة في مراقبة المعالجة الكيميائية لمرضى السرطان في الأردن. تم تصميم استبانه ذاتيه التعبئة مبنية على دراسات رجوعية للتكنولوجيا والمعرفة المتقدمة بخصوص آلية المراقبة السريرية للمعالجة الكيميائية الأكثر استخداماً في حقل السرطان .أجريت الدراسة في الفترة مابين شهر ديسمبر من العام 2009 وشهر فبراير من العام 2010 في اثنين من المراكز الرئيسية لعلاج السرطان في الأردن وقد تبين من النتائج إن الأسلوب الأكثر إتباعا في تقديرات الجرعة المبدئية لا زال مبنياً على مساحة الجسم الكلية (96,8%) بينما أشار (17,5%) و (76,7%) فقط من مشاركين الدراسة بأنه يتم تزويد خدمات مراقبة العلاج الدوائي للأدوية المختصة بمرض السرطان وغير السرطان في المؤسسات التي يعملون فيها، على التوالي. واتضح من نتائج دراسة أن أكثر أدوية السرطان قياساً لتركيز مستواه في الدم هو ميثوتركسيت (n=5) ويليه 5– فلوروبوراسيل (n=3) ، بينما تبين أن أكثر العلاج الكيميائي لغير السرطان قياساً للمستوى الدوائي في مصل الدم هو تاكروليمس (n=22) و سايكلوسبورين (n=22). أقر معظم المشاركين (83,9%) بأنه لا يتوفر لديهم برنامج إلكتروني متخصص لتقدير الجرعات مبنياً على التمثيل الحوسبي لتركيز الأدوية المرئية في الدم. أظهرت هذه الدراسة المقطعية وجود انخفاض ملحوظ في تطبيق نظام مراقبة مستوى الدواء في الدم لدى مرضى السرطان بالمقارنة بالدراسات العالمية مما يحفز ويؤكد ضرورة الشروع ببرامج توعية إضافية عن أهمية هذا النظام على ضوء النتائج السريرية والاقتصادية السابقة وبخاصة فيما يتعلق بالبرامج العلاجية التي سبق وأن أثبت فيها ذلك عالمياً.

الكلمات الدالة: مراقبة العلاج الدوائي، المعالجة الكيميائية السرطانية، الأنظمة متعددة الاختصاص، التدريب المهني، الأردن.

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