

Quality in Oncology Pharmacy

In collaboration with



Editors

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Oncology pharmacy: support for the best quality in patient care

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In oncology care, the five Rs of drug treatment, “the right drug for the right patient in the right dose via the right route at the right time”, is particularly important, considering the narrow therapeutic index of the chemotherapeutic agents with their potential deleterious consequences, the complexity and severity of the disease but also the increasing expectancy of long-term survival.

In this supplement of the *EJHP Practice*, the official journal of the Association of EAHP with more than 22,000 members in Europe, we will demonstrate how collaboration with hospital pharmacists can be of benefit both for the clinical oncologist as well as for the patient. In this special issue, the result of an ongoing collaboration from *EJHP Practice* with ESMO, we will pay attention to four stages in delivering safe and efficacious chemotherapy:

- support in the process of prescribing, like the help of technology, but also dose adjustments in decreased organ function
- background information on drug stability and interactions
- aspects of safe preparation and the use of protective devices
- ways of improved administration of the drug and treatment of extravasation as a complication of wrong administration.

The term “right drug” goes beyond just picking the right drug from the shelf. It implicates that by the time the drug arrives at the patient that the quality is still assured. Many drugs are susceptible to chemical decomposition when formulated in liquid form, particularly after the dilution step required by the preparation of infusions. Such degradations not only lead to a loss of potency of the drugs but may, in some cases, cause intolerance or toxicity. Drug interactions with the infusion solvent or adsorption onto glass and plastic materials such as PVC or leaching of plasticisers can also occur. Physicochemical interactions and subsequent incompatibilities can take place before or during the IV administration of an “in-bag” mixture of drugs. This has become even more important with new long-term infusion technology for ambulatory treatment, when administration (= contact time) can be

extended for 24 hours or more. Therefore, tackling the instability of anticancer drugs in practical situations must be considered not only an important contribution of the pharmacist to the overall quality of patient care but also an underdeveloped area of research that deserves strong development.

When considering preparation, contamination of hospital and pharmacy staff may form an unwanted risk. In many hospitals preparation of cytotoxic drugs is now being centralised (most times in the pharmacy), relieving nursing staff from this burden. Medical oncologists and nursing staff may not be always aware of the different complicating “pharmaceutical” factors when starting chemotherapy, and in this volume we will bring you up to date.

The terms “right patient” and “right time” refer to the idea that the chemotherapy regimens should be adapted to the individual patient, considering metabolism, age, possible organ dysfunction and specific target phenotype. Chemotherapy in elderly patients is particularly interesting, due to the increasing incidence of most cancers with age.

We would like to have included chronobiology, target phenotyping, drug compliance and supporting clinical trials. However, since practical applications of these topics may as yet not be that widespread, the editorial choice was to favour those more representative of the pharmaceutical services that most hospital pharmacies currently can offer. If you have not done so yet, give your pharmacist a call, and start collaboration!

The increasing role of pharmacists in oncology fully justifies oncology pharmacy now being considered a specialist area in several countries, with its own university courses. In Europe, this speciality is strongly supported by the European Society of Oncology Pharmacy, representing 27 countries and now a full member of ECCO. Oncology pharmacy is a challenge that fully justifies our tireless efforts, quality education and good research in the benefit of the best patient care we can offer.

Paris/Rotterdam, August 2008

The role of the oncology pharmacist in the therapeutic decision-making process

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In the increasingly complex field of oncology care, hospital pharmacists should be redefining their role. Their expertise can contribute to decision making in many ways, for example drawing up guidelines, evaluation of daily practices, organisation of care, and the promotion of cost-effective practices.

The systemic treatment of cancer has been evolving constantly for two decades [1]. Many active anticancer agents have become available, covering most clinical situations. With the emergence of targeted therapies and the development of pharmacogenomics, biological and/or cellular parameters are becoming the main factors in therapeutic decision making. Cancer is now considered a chronic disease and many patients can hope for successive lines of active treatment for advanced stages of their disease [2]. So defining the best strategy for each patient is now a complex challenge. In this context, the decision-making process has to be adapted to new parameters and constraints and the role of the oncology pharmacist should be reviewed.

The necessity for, and benefit of, multidisciplinary practice in cancer is accepted. The role of pharmacists in anticancer drug compounding is undisputed. Their place in drug monitoring and prevention of medication errors is also accepted [3]. On the other hand, looking at the literature, the involvement of pharmaceutical expertise in therapeutic choices is scarcely considered, with the exception of pilot studies in supportive care [4, 5]. Considering the complexity of appropriate use of drugs in cancer, the position of oncology pharmacists in decision making should be complementary and useful to oncology practice. Their expertise can be developed in many directions contributing to decision making: drawing up guidelines, evaluation of daily practices, organisation of care, and promotion of cost-effective practices [6].

The definition of appropriate use of drugs is a major challenge in cancer. With intensive clinical research in the area, available data have dramatically increased. Daily practice has to be related to evidence-based medicine [7]. Although several therapeutic options are frequently open to the cli-

nician, randomised clinical trials are not always accessible. A recent review showed that the pertinent information about efficacy was reported in less than half of publications on the most common tumours such as lung, breast, colorectal and ovarian cancer [2]. Although strategy trials, including successive treatments, are now mandatory in metastatic situations, a large body of published data remains related to drug trials. Finally, as off-label use of drugs appears to be inevitable in cancer, it should be controlled and justified [8].

In France, several cooperative, multidisciplinary studies have compared daily practice to published data in solid tumours. Recently, we conducted a retrospective study in two specialised centres, including 1,561 consecutive adult patients with solid tumours [9]. Although off-label use amounted to 33% of cases, 78% of observed treatments were supported by results of phase II (4%) or phase III (74%) randomised trials at the time of use. Furthermore, 20% of additional use was supported by one (4%) or several (16%) positive phase II trials. Finally, the level of questionable use was limited to 2% of cases in this study. The multivariate analysis showed that level of evidence of individual choices was significantly dependent on type of tumour ($p < 10^{-3}$) and stage of disease ($p < 10^{-3}$). In another study, Debrix et al. likewise estimated the level of questionable use at 2%, based on the opinion of an independent expert committee [10]. These multidisciplinary studies, conducted by pharmaceutical teams, confirmed the limits of official labelling of drugs and the necessity for professional guidelines. Recently, a medical and pharmaceutical committee has been set up by the French National Cancer Institute [11]. Its objective is to define guidelines for appropriate use of anticancer therapies. This is a particular challenge for advanced stages and uncommon cancers. Interestingly, these guidelines include off-label use supported by a sufficient level of evidence.

The difficulty of applying published guidelines in daily practice is widely demonstrated in health care. In France, payments for expensive hospital therapies, such as anticancer drugs, are now conditioned by national guidelines. The oncology pharmacist may have a considerable role, especially in organising care. In local settings, a register of valid chemotherapy schedules is mandatory for each tumour, linked to electronic prescribing [5]. The same objective of standardised practice is now being set within regional oncology networks [12]. Oncology pharmacists are allowed to take part, indeed they are invited to coordinate these actions, which contribute to promoting standard guidelines in daily practice.



For instance, in the Franche-Comté area (1.2 million inhabitants), our pharmaceutical team is mandated by the regional oncology network to coordinate the regional guidelines committee, as well as to evaluate the conformity of daily practice to several guidelines. Additionally, as use of outside guidelines appears to be inevitable in oncology, these situations have to be assessed and benchmarked by multidisciplinary teams, including oncology pharmacists.

The last area favourable to develop pharmaceutical expertise in decision making is pharmaco-economics. If new therapeutic

options significantly improve the prognosis for diseases, the costs of treatment are dramatically enhanced. Economic benefit/cost studies are required to optimise the consumption of healthcare resources. Cost-effectiveness data should be integrated into the decision-making process [2]. While the number of published studies has increased in cancer treatment, the number of pharmaco-economics studies remains low [13]. The use of economic evidence in decision making appears to be uncommon [14]. It seems that these studies are still considered a brake to medical progress. Additionally, their results often fail to represent daily practice [2]. The oncology pharmacist has to develop more pragmatic and comprehensive economic studies, if we are to

influence decision making. For instance, areas ripe for investigation include the economic impact of overall treatment strategies, alternative schedules or the advantages of ambulatory chemotherapy [15].

In conclusion, the appropriate use of anticancer treatments is a common objective, from both the patient and the health authorities' point of view. Oncology pharmacists can play a decisive role, from drawing up guidelines to evaluating daily practice. Our challenge is to legitimise pharmaceutical expertise within multidisciplinary care.

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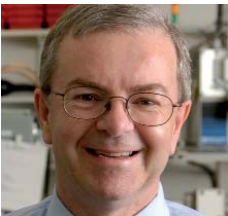
The use of medication safety technology to deliver safe use of medication

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Brigham and Women's Hospital (BWH) has invested substantial time and resources into computerised physician order entry (CPOE), bar code scanning, chemotherapy order templates for high-risk protocols and clinical trials, smart infusion pump technology and medications reconciliation systems.

Brigham and Women's Hospital is a large academic tertiary teaching hospital in Boston, MA, USA. Our 747-bed institution has an average of 95 patients per day for haematology, oncology and haematopoietic stem cell transplant services. The adult inpatient oncology service is a collaboration between Dana-Farber Cancer Institute and BWH.

A balance of strategies

Several strategies are used to decrease medication errors. These include the use of information technology such as CPOE, multidisciplinary patient care teams, oncology pharmacy specialists, smart infusion pumps, electronic medication administration records and bar code medication administration verification. The medication administration system combines use of these strategies and technologies with medication reconciliation software and adverse drug event (ADE) surveillance systems.

Technology is only part of the answer for medication safety. A diverse team of highly skilled oncology clinical pharmacists, nurses and physicians is also essential. Research shows that pharmacists can help decrease the number of ADEs by participating in daily rounds [1]. This is done at BWH, by providing medical team education, drug information, medication order review and identifying and preventing ADEs.

The use of CPOE

Prescribing errors have been identified as preventable events in the medication administration process [2]. CPOE may substantially reduce ADEs and/or errors, including omissions [3, 4]. Its use requires a significant investment in resources [5] but this has been shown to improve the overall quality of patient care and patient safety [6]. Oncology providers use it to effectively, safely and efficiently order chemotherapy agents and associated support care medications. Our

chemotherapy order entry (COE) system was introduced in 1997 after several trial periods. It helps ensure patient safety by providing electronic protocol templates and order sets for high-risk patients including all haematopoietic stem cell transplant regimens. A novel feature of our COE system is automatic prompts to prevent omissions. For example, when entering a chemotherapy order set, the physician is required to enter height and weight, criteria to initiate treatment, hydration and anti-emetics. Other safety features include specific dose limits for chemotherapeutic agents, restriction of order writing privileges and drug-allergy, drug-dose and drug-interaction checking.

Once an attending level physician with chemotherapy writing privileges has entered a chemotherapy order set, the nurses verify it with the patient's height and weight. If the weight entered by the nurse results in a dose discrepancy $\geq 5\%$, the order set will need to be reviewed and approved by the oncologist.

After the nurse verification, the clinical pharmacist reviews the order for correct dosage according to a protocol. A second clinical pharmacist reviews the order set against laboratory parameters and a reference and then authorises the preparation of the chemotherapy. A standard chemotherapy dilution guideline is used to help assure consistency and accuracy in preparation. The guideline contains standard drug concentrations, final dilution requirements, standard fluid admixtures and infusion rates. Additionally, clinical trials and approved regimens are maintained in an electronic database as a reference for physicians, nurses and pharmacists.

Bar codes

Bar code verification has been proved to reduce medication dispensing errors and reduce potential ADEs [7, 8]. Bar code verification is needed both

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Figure 1: The prescriber is prompted to prescribe pre-hydration fluids, hydration fluids and antiemetics where appropriate

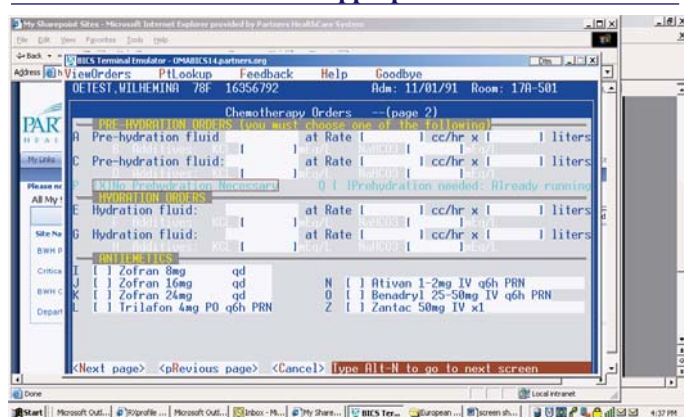
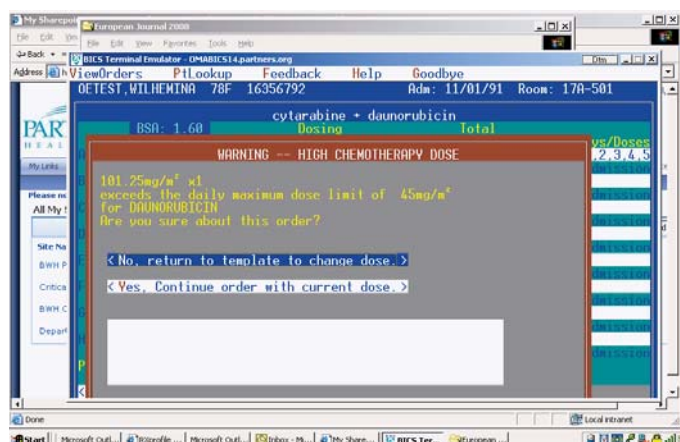


Figure 2: A warning is given for an unusual dose of chemotherapy



in the pharmacy during drug preparation and at the time of administration. This helps ensure that the right patient receives the right medication, at the right dose and at the right time. All medication and diluent bar codes should be verified prior to preparing the dose. The pharmacy system should then calculate the appropriate amount of medication and volume to be placed in the syringe or injected into the administration container. In the near future, robots with multiple safety features including bar code verification will be widely available to complete these complex calculations and prepare chemotherapy medications efficiently and accurately.

Barcode Medication Administration (BCMA) needs to be an integral component of any medication administration system. When deciding on a system key decisions will need to be made on the type of bar codes to be used, staff and patient identification bar codes, hardware such as scanners and laptop computers and ultimately the software system. Workflow analysis is essential for all clinicians that use the system so that the technology will complement the daily activities of the end users. End users need to be involved in the hardware and software decisions so the best system for your institution is chosen. The system needs to be easy to use by the end user to prevent possible system workarounds.

Features of the system

The clinician must be given access to all pertinent data such as patient laboratory results, patient diagnoses, physician instructions and drug information when administering medication. In addition, real time hard stop alerts must advise the clinician whether the medication and/or patient is not correct, to stop the clinician from continuing in the administration process. The system should include error tracking reports to allow for continuous assessment of the process and identification of quality improvement opportunities.

Our ongoing analysis of error prevention after BCMA implementation is demonstrating positive results. In February 2008,

our system intercepted 5,824 potential wrong drugs, 137 instances of wrong patient and 314 instances of expired medications. BWH believes that these are potential medication errors that were prevented by our system.

Once the chemotherapy dose is delivered to the nursing unit, the chemotherapy orders are compared with an online oncology reference and verified by two nurses. Ideally, BCMA must be linked to a smart pump to infuse the chemotherapy.

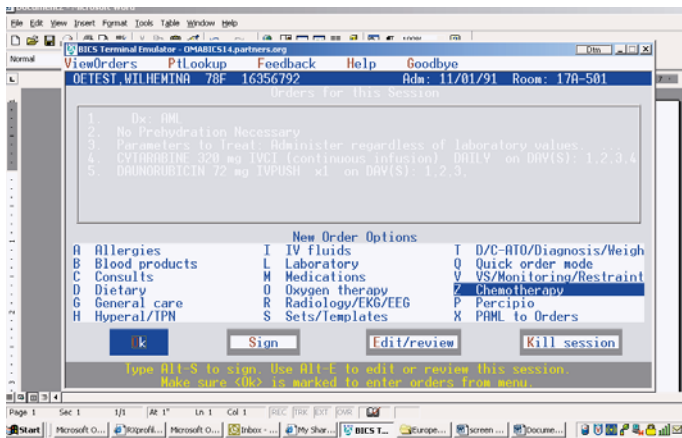
In smart infusion technology, IV infusion devices contain a point of care clinical guidance system or drug library. The drug library is a list of parenteral medications and their admixture concentrations that at the time of IV administration provide the user with information and guidance around best practice. The software within the smart pump alerts users to potential or actual administration errors. Features include creation of an institution-defined or standardised parenteral admixture list, protection around high and low infusion rates, documentation of drug library usage and quality data that can be reviewed.

When rolled out, the pump software did not allow for body surface area dosing and dose over time programming. The software was upgraded in May 2007 and BWH was able to compare “before” and “after” data.

To prepare for the upgrade, a multidisciplinary implementation team was created consisting of the institution’s experts in the smart infusion pump, nursing and clinical oncology pharmacy. Standardised rules for creation of drug entries were established with regard to naming and dosages of drugs. For many chemotherapeutic agents there is wide variation in dosing. To create wide high and low infusion rate limits would render the rate protection of the smart pump ineffective. It was decided that dose ranges would need to be split up, to create more meaningful dosage and infusion rate parameters and avoid in-range programming errors on the pump.

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Figure 3: The range of options a chemotherapy prescriber is prompted to consider



Continuous Quality Information (CQI) can be downloaded from smart pumps. CQI contains information regarding drug library usage, user programming, and prevention of errors. Review of CQI data provides the opportunity for members of hospital safety committees to improve the drug library and identify opportunity for process and systems analysis and improvement. Data from CQI analysis portrayed the impact of the upgraded software as use of the drug library went from 4.14% of chemotherapy infusions to 74.56% of infusions with the implementation of the new data set.

Future directions

Significant changes to the chemotherapy medication order approval and administration process will be introduced in 2009. Software upgrades to the pharmacy system will include robust medication administration scheduling software designed to handle the most complex of chemotherapy regimens or protocols. New functionality will be added to both the COE system and the pharmacy system: for linking related medication orders, sequencing of medication orders with regard to administration and preparing and administering split doses and multiple medications that are administered as one combined dose.

As well as coping with custom schedules for more complex chemotherapy, it will enable the pharmacist to link the anti-

emetics and hydration administration times with that of the chemotherapy. Working in collaboration with the unit-based pharmacist, the nurse will be able to edit chemotherapy administration times to meet special needs and will be prompted regarding the sequential administration of hydration, antiemetics, and chemotherapy at the bedside. The system will work through pre-programmed prompts using our existing bar code verification and BCMA technology.

The BWH pharmacy is currently evaluating the use of a robot to prepare all our inpatient chemotherapy doses. We anticipate completing our clinical trial of this device by the end of 2008 with full rollout in early 2009. In addition to the robotics, BWH is introducing the use of a bar code-driven system for disposing of hazardous pharmaceutical waste including chemotherapy waste. The EcoRex is a four-compartment waste system using the scan, dispose and close concept. It contains a proprietary database of 145,000 drug identification numbers and eliminates institutional database management. Bar code verification guides the user to the proper waste stream. The machine reads both one-dimensional and two-dimensional bar codes and alerts the user when the waste container is full.

The final step is to “close the loop” of our medication administration system by assuring full bi-directional connectivity between our CPOE, pharmacy, smart pump platform and BCMA systems. This will help to assure that critical medication information is flowing between all platforms in real time.

Conclusion

Over the years, the complexity and dosing of cancer treatment have increased. Protocols and clinical trials are complicated and often involve the use of multiple drugs given at various doses and schedules. Technology is important and crucial to the practice of pharmacy and medicine but it is only useful when used with skilled pharmacists, nurses, and physicians to ensure the safety and accuracy of patient care. Using all of these features together will help BWH reach its goal of a seamless digital pathway from prescription to patient and ensure accuracy of medication dosing and administration, resulting in positive patient outcomes.

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Chemotherapy dose modification according to organ function and pharmacokinetics

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Chemotherapy dosing is complicated by variable effects and low therapeutic indices, and dose optimisation data for specific patient groups are often sparse. This article discusses some benefits and limitations of pharmacokinetically guided dosing and dose modifications used in organ impairment.

Introduction

Among all drug classes in clinical use, cancer chemotherapy drugs generally have the lowest therapeutic index and perhaps the most extreme toxicity, often caused by cytotoxic effects on healthy tissues. Selective targeting of malignant tissues is therefore a key focus of research. Compared with the increased knowledge gained around the genetics and molecular biology involved in tumour growth, the success of translating this information into therapies has been moderate and the number of novel drugs reaching the clinic is limited. Although the use of more recently approved drugs such as the monoclonal antibodies is increasing, the cytotoxic chemotherapy drugs continue to be the most commonly used therapeutic agents in the treatment of cancers and this is unlikely to change in the near future. The general consensus that the clinical value of targeted therapies may be best exploited as a complement to traditional chemotherapy or radiotherapy supports this view.

temporary practice are still based on the traditional BSA. These doses are frequently reduced because of intolerable toxicity, previous chemotherapy/radiotherapy, organ impairment, age or obesity, although treatment delay is a common alternative in some of these scenarios.

Dose modifications according to organ impairment

In general, cytotoxic drugs are marketed with limited information on drug PK/PD in patients with hepatic or renal dysfunction and in clinical practice, dose modifications are usually performed as recommended by local guidelines or the drug SPC. Most commonly, doses are reduced by fractions, for instance, 25% or 50%, based on the degree of organ impairment and extent of hepatic or renal clearance (CL) for the specific drug. Considering the current lack of evidence for more individualised adjustments, this is probably the most rational approach. Besides, standard tests

BSA-based doses fail to reduce the variability in PK and PD for the majority of drugs in adults.

Chemotherapy dose selection remains an important and complex issue because cytotoxic drugs exhibit a narrow therapeutic window together with large intra and inter-patient variability in pharmacokinetics (PK) and pharmacodynamics (PD) [1]. With the aim of optimising these variable therapeutic effects and minimising toxicity, dose individualisation based on body surface area (BSA) has been practised for many years. Although studies at the time indicated that this approach was useful [2], current research indicates that BSA-based doses fail to reduce the variability in PK and PD for the majority of drugs in adults [1]. Due to the lack of alternative dosing strategies, with some exceptions, doses in con-

used for assessing hepatic and renal functions are not exact measures of organ function or how the CL of specific drugs will be affected. While liver function tests reflect liver integrity and, to some extent, metabolic function, they do not enable predictions of specific drug metabolising enzyme capacities. The glomerular filtration rate (GFR) is often estimated, as opposed to measured, using serum creatinine (Cr) in CrCL prediction equations. Various studies have suggested that these equations have several drawbacks and that estimated GFR is inaccurate in many patients because serum Cr levels may be affected by diet, drugs, age, obesity, cachexia and diseases, for example malignancies [3]. Gold standard tests for

GFR such as isotopic or inulin CL methods are clearly not available in all settings, so the important point to grasp is that estimates have limitations and must be evaluated with reference to the full clinical picture.

Considering these issues, the direct determination of PK in patients with organ dysfunction would be the most accurate approach. For drugs with linear PKs, the PK following sub-therapeutic test doses could guide the selection of therapeutic doses. However, although this would facilitate dose reductions that are proportional to the decrease in drug CL compared with that in the 'average' patient, the discussion in the following section addresses why it would not necessarily enable a more exact prediction of the clinical effects.

Dose modifications according to drug levels or PK

The monitoring of either plasma drug/metabolite levels (therapeutic drug monitoring, TDM) or PK measures are examples of more modern strategies that are sometimes discussed in relation to chemotherapy dosing [4, 5]. Alternatively, a more straightforward approach is to assess specific enzyme functions to predict drug PK. For example, dihydropyrimidine dehydrogenase and uridine diphosphate glucuronyltransferase 1A1 deficiencies can be measured or detected with genotyping prior to 5-FU and irinotecan treatment [6].

Drugs for which TDM and PK-guided dosing have proven valuable include methotrexate and carboplatin. Methotrexate levels may be monitored to aid dosage adjustments of folinic acid "rescue", while carboplatin is dosed to achieve a pre-defined area under the plasma concentration-time curve (AUC) based on the relationship between the AUC and therapeutic and toxic effects [4, 7]. Determination of drug levels and subsequent PK modelling are not necessary for carboplatin on a routine basis, as the AUC can be predicted from the correlation between GFR and carboplatin CL [7]. For many other drugs, real-time measurements and PK data analyses are required. Due to advances in analytical methods for the determination of drug levels in tissues this is generally achievable, although practical and economic issues are clearly involved. It

should, however, be recognised that chemotherapy drug exposure or plasma levels may not predict clinical outcome and for a large number of drugs there are no, or very poor, correlations between drug levels or PK measures and PD outcomes [1]. In addition, any relationships observed between PK and PD in specific trials may become further confounded by patient and disease-specific factors such as age, the use of concomitant drugs, differences in intra-tumour PK and drug resistance [1]. For example, elderly patients may have PD alterations that are not reflected by any changes in PK [8]. Therefore, although PK monitoring can be useful to facilitate the standardisation of drug exposure within or between patients, it is not straightforward to evaluate target exposures for all drugs or when PK/PD data are insufficient.

Patients who could benefit from PK monitoring are the obese. Obese patients frequently have substantial first-cycle dose reductions when they receive doses which are 'capped' at a BSA of 2–2.2 m², without any evidence suggesting an increased exposure compared with normal weight subjects. In fact, it has recently been shown that the CL of several chemotherapy drugs is not reduced in these patients and that capping may result in suboptimal treatment outcomes, which makes this an important area for further research [9]. Even if there may be no known target exposures to aim for, the evaluation of PK data would at least indicate if these patients are exposed to drug levels that are similar to, higher or lower than those in lean patients, and this could subsequently help inform dosage recommendations.

Conclusion

The use of standard tests to assess organ impairment and the application of adaptive methods for chemotherapy dose modifications have both advantages and limitations, some of which are discussed above. It is clear that modern approaches to dose individualisation may be beneficial in specific settings, while the rationalisation and introduction of standardised doses may be adequate in others [4]. Regardless of which, when dose modifications have been made, appropriate clinical follow-up and subsequent adjustments, either downwards or upwards, are essential.

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Chemotherapy in the elderly: the critical factors

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The geriatric population is *a priori* a heterogeneous population at all levels, and therefore it is difficult to provide simple guidelines. A detailed knowledge of individual drug profiles is viewed here through the prism of the purpose of the treatment and specific effects of ageing.

Introduction

Most patients with cancer are elderly; but most clinical trials are done on younger people. How are we to tackle the paradox of there being most need in exactly the population for which there is least guidance? Furthermore, the elderly are the most heterogeneous group of patients. Older patients differ more from one another than do younger individuals, by virtue of individual processes of reduction in functional status and the accumulated effects of multiple comorbidities. Therefore this group (broadly, those over 70 years of age) are at greatest risk of toxicity and drug-drug interactions.

A first step is to define the goal of therapy. In very frail patients with considerable comorbidity, supportive care is often the best course of action, even if tumours are potentially curable. If the patient has incurable metastatic disease, palliation may be the best course, and treatment should be cautious enough to avoid toxicity. This still leaves two settings in which effective treatment is desirable: curative and adjuvant (Table 1).



Having decided to treat the patient actively for the cancer, there are two main avenues to explore in coming to the best dosage regime: the characteristics of the specific chemotherapeutic agent(s)

Table 1: Purpose of treatment in elderly cancer patients [1]

	Curative setting	Adjuvant setting
Setting	Curative intent in advanced disease	Curative intent in (possibly) micro metastatic disease
Examples	Germ cell tumours, lymphomas	Adjuvant setting in breast cancer, colon cancer, ovarian cancer
Attitude	Some toxicity is acceptable, if it is well managed	Always weigh advantage (usually rather small) versus disadvantages (toxicity, morbidity of treatment)
Dose intensity	Aim to maintain dose-intensity to optimise chances of cure, but remember pharmacological principles and alterations in the elderly	Dose intensity can be very important in order to have any gain at all, but remember pharmacological principles and alterations in the elderly

Parameter changes	Clinical consequences
Absorption: decreased	Oral chemotherapy, e.g. capecitabine, might be less effective in the elderly
Volume of distribution: decreased	Serum concentrations and toxicity of several chemotherapeutics might increase, e.g. cisplatin, taxanes, etoposide, irinotecan
Hepatic metabolism: decreased	Not well known, may affect serum concentrations of chemotherapeutics eliminated by hepatic metabolism, e.g. taxanes, cyclophosphamide, anthracyclines
Renal excretion: decreased	Dosing should be adapted to present recommendations in order to avoid excessive serum concentrations and toxicity from renally excreted chemotherapeutics, e.g. carboplatin, topotecan, methotrexate

Table 3: Main age-related pharmacokinetic effects on frequently-used chemotherapeutic agents

Drug	Effect
Cyclophosphamide	Adapt to renal function, check toxicity if liver function is reduced
Ifosfamide	Increased area under the curve (AUC), consider protracted infusion
Melphalan and dacarbazine	Adapt to renal function
Temozolomide	No evidence for <i>a priori</i> dose reduction in elderly
Cisplatin	Increased AUC and toxicity, consider lower dose and slower infusion
Carboplatin	Adapt to renal function
Vinorelbine	No evidence for <i>a priori</i> dose reduction in elderly
Paclitaxel	No evidence for <i>a priori</i> dose reduction in elderly
Docetaxel	Pharmacokinetics (PK) minimally affected by age
Etoposide	Increased AUC and toxicity
Irinotecan	Increased AUC and diarrhoea, consider a lower dose
Topotecan	Adapt to renal function, consider weekly regimen
Methotrexate	Adapt to renal function
Fluorouracil	PK and toxicity not greatly affected
Capecitabine	Lower dose seems equally effective with lower side effects
Gemcitabine	Generally well tolerated in the elderly
Fludarabine	PK and toxicity not greatly affected
Doxorubicin	At full dose relatively toxic: reduce dose, change formulation or omit
Idarubicin	Adapt to renal function, little reliable data
Mitoxantrone	No evidence for <i>a priori</i> dose reduction in elderly
Bleomycin	Adapt to renal function

and the characteristics of the individual patient. In general, and for most drugs, age itself is not a contraindication to full dose chemotherapy. Cancer chemotherapy in the elderly can best be considered as an example of the need for dose optimisation in individual patients.

Ageing factors specific to chemotherapy drugs

Clinical data exists of factors that can influence the pharmacokinetics of specific anticancer drugs frequently used in the elderly, and the clinical or biochemical parameters that could form the basis for dose adjustments with age [1, 2]. Table 2 gives some examples. However, generalised dose adaptation based on age-related pharmacological changes is an unvalidated approach since clinical trials are lacking. The International Society of Geriatric Oncology (SIOG) is also currently developing recommendations on this topic [3]. So further age-related effects on pharmacokinetics need to be taken on a drug-by-drug basis. Table 3 briefly indicates the current knowledge for some frequently used chemotherapeutics.

Older cancer patients undergoing classical chemotherapy are at higher risk of experiencing toxicity. However several studies show that chemotherapy is generally well tolerated with a limited impact on independence, comorbidity, and quality of life. Hormonal therapy or new molecular approaches such as signal transduction inhibition are promising in the elderly, because of the frequent lack of side effects associated with classical cytotoxic drugs. Examples of effective and generally well tolerated new targeted therapies that might be used as monotherapy or in combination with “soft” chemotherapy include trastuzumab in Her2 positive breast cancer, cetuximab, concomitant with radiotherapy in head and neck cancer, bevacizumab in colorectal cancer, imatinib in chronic myeloid leukaemia.

Assessment of the ageing individual

Because elderly people vary so much, cancer chemotherapy in the elderly can best be considered as an example of the need for dose optimisation in individual patients. In general, and for most drugs, age itself is not a contraindication to full dose chemotherapy. The main limiting factors are comorbidity and

poor functional status, which may be present in a significant number of the elderly population.

If initial screening of the patient's status is positive, it should be followed by a more complete geriatric evaluation. A comprehensive geriatric assessment, evaluating functional status, comorbidity, socio-economic conditions, nutrition, polypharmacy, and the presence or absence of geriatric syndromes, is indispensable in the treatment of elderly cancer patients [5] and has been shown to improve therapeutic outcome [6]. Biological and clinical markers for "degrees of ageing" include albumin, haemoglobin and creatinine clearance, a functional status assessment and screening for depression and cognitive impairment.

Further common sense tips include beware of drug interactions, monitor compliance and maintain adequate hydration.

Elderly patients have a tendency to drink less, especially when feeling ill, but are less tolerant of dehydration. Adequate oral fluids should be specifically advised for older cancer patients during treatment with anticancer drugs.

Conclusion

The management of the elderly patient with cancer presents an increasingly common challenge. The elderly will often be the largest group of patients treated by the medical oncologist. When prescribing chemotherapy, the aim of chemotherapy should be specified since it can have impact on the choice of dosing. Oncologists should be familiar with the age-related changes in physiology that affect the disposition and response to drugs in older patients. In general, and for most drugs, age itself is not a contraindication to full dose chemotherapy.

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Drug interactions in oncology

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Drug-drug interactions are always of concern in drug therapy, but especially in oncology. The various types of drug interactions are presented, with selected examples. Vigilance is always required as so many interactions are possible that they are not always predicted.

Cytotoxic anticancer drugs are amongst the most potent medicines and have complex pharmacology: a narrow therapeutic window, a steep dose-toxicity curve and great intra- and inter-patient pharmacokinetic and pharmacodynamic variability. Polypharmacy is the rule rather than the exception in oncology. Not only “chemo cocktails” are administered but also drugs to reduce the toxic side effects of the chemotherapy and provide palliation. Drug interactions can be divided into pharmaceutical, pharmacokinetic and pharmacodynamic interactions. These can be wanted or unwanted, between cytotoxic drugs, between cytotoxics and non-cytotoxics, and possibly with pharmaceutical vehicles. Potential interactions between anti-cancer drugs and over-the-counter (OTC) or alternative medicines and herbs should not be underestimated. More attention should be given to the recognition of potential drug interactions in the development phase as well as in daily practice. Pharmacists are well equipped for this task.

Pharmaceutical interactions

These occur when two compounds interact because of their physico-chemical properties. Examples are physical or chemical incompatibilities when admixtures are prepared for infusion. When the thiol mesna (sodium 2-mercaptoethanesulfonate) is added to a cisplatin solution it inactivates the platinum drug by forming a covalent mesna-platinum adduct. Mitomycin C rapidly degrades into inactive mitosenes when dissolved in 5% dextrose infusion fluid (pH 4-5). Taxanes, epipodophyllotoxins (after dilution) and 5-FU (at low pH) tend to precipitate in infusion fluids.

An example of a wanted pharmaceutical interaction is the modulating effect of a vehicle on the pharmacokinetic, and by that the pharmacodynamic, properties of a drug. Doxorubicin encapsulation into pegylated liposomes (Doxil, Caelyx) results in a lower incidence of cardiotoxicity and has a huge

impact on the pharmacokinetic profile of the drug. As a consequence the dose-limiting toxicity profile has changed from bone marrow suppression and cardiac toxicity with free doxorubicin to palmar plantar erythrodysesthesia.

Taxol contains the cytotoxic active ingredient paclitaxel, which is solubilised with a mixture of polyoxyethylated castor oil (Cremophor EL) and ethanol. The vehicle markedly affects the pharmacokinetic behaviour of paclitaxel. When Taxol is combined with other drugs, e.g. doxorubicin, this “Cremophor EL effect” should be taken into account. Obviously a pharmaceutical vehicle cannot always be considered a physiologically inert additive.

Pharmacokinetic interactions

Many drug-drug interactions are pharmacokinetic and one drug affects the disposition of the other. They involve the four basic, almost indistinguishable, kinetic principles: absorption, distribution, metabolism and elimination (ADME). Metabolising enzymes and/or drug transporters are often involved in these processes.

Absorption

The oral bioavailability of 6-mercaptopurine rises substantially when the drug is combined with allopurinol. Allopurinol inhibits the enzyme xanthine oxidase in the intestinal tract and liver that converts 6-mercaptopurine into the inactive 6-thiouric acid. During combined use this oxidative catabolic pathway of 6-mercaptopurine is inhibited, slowing its breakdown. Thus it becomes more available for anabolic conversions by which cytotoxic products are formed, in particular 6-thioguanine. This interaction may lead to serious side effects (bone marrow suppression and liver damage) with sometimes a fatal outcome. If in spite of this the combination is desired, the dose of 6-mercaptopurine should be reduced to 25-33% of normal. This interaction also occurs with azathioprine, a prodrug of 6-mercaptopurine.

Distribution

Anticancer drugs can bind to several blood components such as albumin, α_1 acid glycoprotein, lipoproteins, immunoglobulins and erythrocytes. The unbound drug is considered the biologically active fraction because it can pass out of the vein to target tissues. Theoretically, displacement from blood components or tissue binding sites by another drug increases the apparent volume of distribution. Displacement is usually of no clinical relevance however, with the possible exception of methotrexate.

Metabolism

The CYP3A4 system is notorious for causing cytotoxics and non-cytotoxics that share the same clearance machinery to interact. Anticancer drugs that are (partly) metabolised by CYP3A4 include the oxazaphosphorines (cyclophosphamide, ifosfamide), the oral tyrosine kinase inhibitors (imatinib, erlotinib) and the taxanes (paclitaxel, docetaxel). Patients are at risk when these agents are given with other CYP3A4 substrates or inhibitors such as benzodiazepines, antifungals, HIV protease inhibitors, antihistamines, immunosuppressants and anticonvulsants.

Understandably, there is always concern about drug-drug interactions with oral anticoagulants. Reported interactions include those between warfarin, 5-FU, capecitabine, paclitaxel, ifosfamide/mesna and etoposide/carboplatin. Even minidose (1 mg/day) warfarin prophylaxis for catheter-associated thrombosis is accompanied by a high incidence of international normalised ratio abnormalities particularly in patients receiving 5-FU, folinic acid and oxaliplatin.

eliminated by the kidneys by both glomerular filtration and active tubular secretion. Thus most interaction concerns relate to the renal handling of these compounds. Drug-drug interactions generally involve renal injury either by the drug itself or the concomitant (nephrotoxic) medication. Probenecid, salicylates and trimethoprim/sulfamethoxazole can increase methotrexate plasma concentrations to toxic levels. Nonsteroidal anti-inflammatory drugs (NSAIDs) have caused (lethal) toxicity when given with methotrexate or cisplatin. Cisplatin can alter the renal clearance of lithium and topotecan.

Pharmacodynamic interactions

When two drugs show no pharmacokinetic interactions they may still affect one other pharmacodynamically (toxicity/antitumour activity) in an additive, synergistic or antagonistic manner. Combination chemotherapy is often preferred to circumvent resistance, to reduce (non-overlapping) toxicity and to gain benefit from any synergistic antitumour action as a wanted pharmacodynamic interaction. For example 5-FU therapy is potentiated by biochemical pharmacodynamic modulation with N^5 -formyl-tetrahydrofolate (leucovorin).

Drug interactions with OTC and alternative medicines

There is particular concern about the risks associated with alternative (herbal) medicines, OTC products, e.g. vitamins, NSAIDs, nutritional supplements and foodstuffs, e.g. grapefruit juice, when they are used in combination with chemotherapy. It can be expected, of course, that any of these interactions are grossly under-reported. High dose vitamin C acidifies urine and may give

Polypharmacy is the rule rather than the exception in oncology.

The CYP3A4 system is notorious for causing cytotoxics and non-cytotoxics that share the same clearance machinery to interact.

In Japan, 15 cancer patients with herpes zoster died after the combined use of oral 5-FU prodrugs, e.g. tegafur, and the new oral antiviral agent sorivudine (*E*)-5-(2-bromovinyl)-1- β -D-arabinofuranosyluracil. They died with a typical picture of 5-FU overdose with diarrhoea, mucositis, leucopenia and thrombocytopenia. Follow-up toxicological investigations in rats revealed that sorivudine is converted into (*E*)-5-(2-bromovinyl)uracil by the gut flora. This compound forms a reactive intermediate which irreversibly inhibits dihydropyrimidine dehydrogenase and explains the 5-FU toxicity. These fatalities might have been prevented if more careful consideration had been given to safety/risk assessments of drug interactions when the antiviral was being developed.

Elimination

Most anticancer drugs are eliminated through metabolism. Platinum compounds and methotrexate however are mainly elim-

rise to acute, life-threatening renal insufficiency when combined with methotrexate, requiring rescue treatment. A pharmacokinetic interaction between St John's wort and irinotecan has been described.

Conclusion

Drug interactions with anticancer drugs are frequently encountered, some with major clinical consequences. Careful preclinical and clinical research has made most combinations manageable in daily practice; however unexpected reactions may still occur. Alertness of patients, pharmacists and physicians remains imperative.

Note: *The subject has been published earlier by the authors in an extended form; see also for references (Beijnen JH, Schellens JHM. Drug interactions in oncology. Lancet Oncol. 2004;5:489-96).*

Information about the stability of oncology drugs: the hospital pharmacist's role

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In general, manufacturers provide minimal information about stability or compatibility. Many stability studies have been performed by hospital pharmaceutical teams to solve everyday problems for preparations.

Many factors can affect the stability of preparations such as the solvent (effect of chloride ion concentration, pH), the light, temperature, concentration and container. These factors have to be taken into account to determine the shelf life of the drug in daily practice. Each preparation (syringe, infusion) has to keep its physical and chemical properties from when it is prepared to the end of administration to the patient.

In general, manufacturers provide minimal information about stability. The stability data stated are often shorter than they really are, e.g. four hours for docetaxel infusions, or do not solve the practical problems (they relate to a special solvent, new container, low or high concentration, etc.). It is therefore the pharmacist who is responsible for retrieving and interpreting existing stability and compatibility data or for performing such studies in the pharmacy itself.

Stability of cytotoxic drugs

There are many reasons for studying the stability of cytotoxic drugs.

To extend the shelf life. Very short periods of stability do not give time for preparation, transport and administration of the drug. For example, the manufacturer says docetaxel is stable for four hours. Two studies have demonstrated a stability of one month for this drug [1, 2].

To allow treatment to be prepared for the weekend or the treatment cycle. In haematol-

ogy, chemotherapy often continues for five or seven days. In the treatment of acute myeloblastic leukaemia, protocols include cytarabine over four or seven days combined with an anthracycline such as daunorubicin or idarubicin. Cytarabine has been shown to be stable enough (29 days) to allow the preparation of the complete cycle [3]. Other publications allow the advance preparation of anthracyclins [4, 5]. Many infusions have demonstrated sufficient stability to be prepared in

advance for the weekend. A non-exhaustive list includes carboplatin, cisplatin, cyclophosphamide, etoposide phosphate, fluorouracil, gemcitabine, ifosfamide, mitoxantrone, oxaliplatin and vinca alkaloids [6-15].

To demonstrate the stability of paediatric preparations. Only a

few dosage forms are

suitable for use in children. Stability studies have been carried out for solutions or suspensions of cyclophosphamide, etoposide, tioguanine, busulfan, chlorambucil and melphalan [16]. Mercaptopurine capsules prepared in the pharmacy have been shown to be stable for one year [17].

To increase patient comfort. The best known example is the old VAD regimen which combined vincristine 0.4 mg/day and doxorubicin 9 mg/m²/day as a continuous IV for four days. This regimen was a common treatment for multiple myeloma. The patient had to stay in hospital to receive two continuous infusions a day. To avoid this, studies were performed to demonstrate the stability of the admixture (vincristine, doxorubicin with sodium chloride) to allow it to be given



on an outpatient basis [18-20]. Today this regimen is prescribed less but these stability studies were of great importance for the quality of life of the patient for many years.

To facilitate administration on the ward. Knowing that mixtures such as cyclophosphamide and mesna [21] or cytotoxic and antiemetic drugs [22] are stable facilitates administration for nurses and patients.

To save money. The most recent example is the study of the stability of bortezomib. Bortezomib is available in lyophilised form in vials of 3.5 mg (Velcade). However, the dose is 1.4 mg/m². For a patient with a body area of 1.8 m², the dose will be 2.5 mg. Therefore, the waste will be one milligram. As a 3.5 mg vial costs Euros 1200, Euros 340 is wasted!

Moreover, neurotoxicity often forces the physician to reduce the dose to 1 mg/m² or 0.7 mg/m², with greater waste. Recent studies have demonstrated that the solution in the vial is stable for at least one week, allowing considerable cost savings [23-25].

To prepare for “dose banding”. Doses of cancer chemotherapy are now being standardised. The preparation in advance of a range of solutions needs them to be stable for two or three months. Carboplatin infusions have been shown to be stable for 84 days [26].

To store vials of monoclonal antibodies at room temperature for short periods. This information may be useful for pharmacists if they have isolators where partially used vials may be stored at room temperature. Biological stability studies are difficult to perform. According to ICH (International Conference on Harmonisation) guideline Q5C, the evaluation of the stability of these compounds may necessitate complex analytical methodologies, so there are very few papers on this subject for hospital pharmacists. A recent preliminary study

[27] suggested that dilute solutions of bevacizumab and cetuximab can be kept for several days at ambient temperature without significant risk of aggregation.

Stability of drugs frequently combined with chemotherapy

Antiemetic therapy. Various studies have evaluated the long-term stability of antiemetics to allow advance preparation and storage in the refrigerator or a freezer for metoclopramide, alizapride, ondansetron and tropisetron [28-30]. Another study demonstrated the possibility of mixing ondansetron, dexamethasone and lorazepam [31].

Adjuvant therapy. Studies have demonstrated sufficient stability for mesna [32], dexrazoxane [33, 34] and sodium folinate [35].

Anti-infective drugs. Long-term stability studies have been performed for voriconazole [36] and aciclovir [37].

Treatment of pain. Many studies have been performed for morphine hydrochloride or sulfate alone or in combination with other drugs [38].

Available stability and compatibility data

Many drug stability studies are published in specialised journals (see references). Stability data for numerous drugs has also been collected in specialised databases from which the user can find information on the effect of various factors (solvent, container, light, temperature, concentration, pH, filters) [38-40].

The STABILIS European database, now freely available on the INFOSTAB website (www.infostab.com) contains 375 injectable drugs including 63 cytotoxic drugs and provides information on the stability in solution and in admixture, on incompatibilities and the factors affecting stability. It is specially designed for the daily practice of hospital pharmacists involved in oncology. It is available in 24 languages and uses pictograms to facilitate communication, Figure 1 shows the screen for the doxorubicin monograph from the STABILIS database (www.infostab.com) as an example. On line five, you can see that doxorubicin solutions 0.04 mg/mL diluted in sodium chloride (green triangle) or 5% dextrose (red lozenge) in PVC containers protected from light are stable for seven days.

These databases are a considerable help for the hospital pharmacist but are not “bibles”. The user can consider them a tool but must have sufficient background knowledge of the design and applicability of stability studies to make an informed decision about their utility.

Conclusion

Stability studies by hospital pharmacists supplement the infor-

Figure 1: A screen from the STABILIS database

Stability in solutions : Doxorubicin hydrochloride						
		2 mg/ml	-20°C		30	740
		2 mg/ml	4°C		180	740
		2 mg/ml	23°C		124	681
		2 mg/ml	4°C		124	681
PVC		0,04 mg/ml	4°C		7	148
PVC		0,1 mg/ml	-20°C		43	686
PVC		0,1 mg/ml	22°C		8	1897

information provided by the pharmaceutical industry (often too restrictive). These studies have allowed us to save money and facilitate preparation by the pharmacy, administration by nurses and the comfort of the patient.

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In vitro drug-drug interactions: how the hospital pharmacist can help

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The theme of stability is further developed in this article, which focuses on *in vitro* drug-drug interactions during ordinary IV infusions and during storage in a portable pump reservoir. Specialist knowledge can be a great help to the patient.

Introduction

Recently much attention has been given to *in vivo* drug interactions, as these are a major cause of morbidity in modern clinical practice, especially in the case of anticancer drugs that have a narrow therapeutic index and are administered to patients taking numerous concomitant medications. However, one must not forget that *in vitro* drug interactions also have a major impact if one is not aware of their existence, or if one does not take precautionary steps. This paper will discuss aspects which require attention with regards to *in vitro* drug interactions and drug-solute interactions (hereafter referred to as pharmaceutical interactions), when administering a combination of drugs in oncology. Examples will be given to illustrate these interactions and attention will be given to ways in which the hospital pharmacist can assist to guarantee the best therapy.

Pharmaceutical interactions

In oncology, a pharmaceutical interaction occurs when two compounds (either two cytotoxic drugs or a combination of a cytotoxic and a non-cytotoxic drug) interact either because they are physically or chemically incompatible. The simplest example is the incompatibility of anticancer drugs with certain infusion solutions, i.e. NaCl 0.9%, dextrose 5%, as such limiting the choice of diluent. More importantly, upon incompatibility of a cytotoxic drug with an infusion solution special attention is required with regards to reconstitution and also with regards to administration; catheters should be flushed with the adequate infusion solution before administration and when switching between different infusion solutions. Examples of such a pharmaceutical interaction include the incompatibility of oxaliplatin [1], amsacrine [2, 3] and (PEG)filgrastim [4] with NaCl 0.9% (drug solubility reduced by chloride ions) and the incompatibility of melphalan and mitomycin with dextrose 5%, leading to rapid degradation of both cytotoxic drugs [5]. Of note,

dilution of melphalan in NaCl 0.9% only marginally reduces this problem [6].

More complex interactions include the incompatibility of drugs in admixtures for infusion. In an ideal situation one might prefer to administer drugs concurrently, i.e. as admixture, as this would reduce infusion and catheterisation time, thus increasing patient comfort and decreasing the chance of infection-related complication. However, due to pharmaceutical interactions, such admixtures are often not possible necessitating sequential administration of drugs. It is interesting to evaluate admixtures in medical oncology such as the combination of a cytotoxic drug and a chemoprotector. An example of such a combination that has been evaluated and proved to be incompatible is cisplatin in combination with mesna in order to limit cisplatin-induced nephrotoxicity: due to the formation of a covalent plat-



inium-mesna adduct cisplatin is inactivated [7, 8] thus interfering with antitumour activity.

A limited number of compatible admixtures of a cytotoxic and chemoprotector are currently used in oncology. The most widely used admixture is 5-FU with low-dose heparin and low-dose prednisolone/hydrocortisone. Superficial vein thrombophlebitis is a common and painful complication in patients undergoing IV cytotoxic, i.e. 5-FU treatment [9] and addition of heparin (1-2 IU/mL) decreases phlebitis and may prolong the duration of catheter patency and decrease infusion failure [10]. However other instances in which the addition of heparin may prove beneficial, such as during dacarbazine administration, have not proved feasible [11]. Instead of the infusion of admixtures, concurrent infusion of two drugs via Y-site injection can sometimes resolve incompatibility issues. For example, for synergistic reasons the cytotoxic drug oxaliplatin is administered in combination with 5-FU and folinic acid (FA, leucovorin calcium). FA and oxaliplatin are incompatible when prepared as admixture, yet Y-site compatibility allows for simultaneous administration of the two drugs [12]. On the other hand, FA and sodium bicarbonate, two drug-drugs used in schedules involving (high-dose) methotrexate, cannot be combined and administered simultaneously due to the precipitation of calcium salts [13].

Medical oncology practice also includes palliative care often requiring (continuous) IV or subcutaneous administration of several opioids and/or regional anaesthetic drugs concomitant-

ly for pain and symptom management. To facilitate treatment in the palliative care setting portable pump reservoirs are often used and *in vitro* drug interaction data are required to ascertain the degree and duration of stability/compatibility. For instance the compatibility of bupivacaine and esketamine is only guaranteed during one hour after admixture [14] limiting the use of this admixture in clinical practice. However, a portable reservoir containing dexamethasone and hydromorphone [15], dexamethasone and morphine [16] or morphine, clonidine and bupivacaine [17] can be administered, based on physical/chemical stability for 24 hours, five days, and seven days respectively.

How can the hospital pharmacist help?

The hospital pharmacist aims to facilitate the safe use of all drugs. One aspect is the safe use of parenteral drugs and includes the assurance of the drug's pharmaceutical integrity including stability and lack of *in vitro* drug interactions. Pharmaceutical companies will seldom put much effort into compatibility, i.e. *in vitro* drug interaction, research. Compatibility data are therefore seldom found in the summary of product characteristics but are sometimes available in specialised handbooks and pharmaceutical journals, easily accessible to hospital pharmacists. With the available information the hospital pharmacist can help to design the best chemotherapy schedule and/or palliative care admixture taking into account pharmaceutical interactions involving drug-drug compatibility's (additive or Y-site), drug-infusion compatibility and drug-container/infusion system compatibility.

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Compatibility of anticancer drug solutions with administering devices

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Interactions between anticancer drugs and their administering devices is a complex and underestimated problem. Interactions can cause lower doses to be administered than intended, drug stability problems or leaching of undesirable components from the plastic into the infused solutions.

The therapeutic advantages of continuous infusion versus intravenous push have been demonstrated for several cytotoxic drugs such as 5-FU, anthracyclines, paclitaxel or vinca alkaloids [1]. Thus, the increasing use of continuous infusion involves a more prolonged contact between drug solutions, i.e. the active principle and the excipients, and the administering devices, i.e. syringes, infusion set, needle, filter, etc., which are now mainly made of polymer materials (plastics). Therefore, the compatibility between the drug solution and the contact materials must be considered. These interactions can be classified in two main classes: uptake of drug by the polymer and leaching of components from delivering devices into the drug solution [2].

Uptake of drug by the delivery device

The uptake of a drug in solution by a solid surface is an interface phenomenon caused by two principal mechanisms: *adsorption* and *absorption*. However, since the distinction between the two processes is not always clear-cut, the noncommittal word *sorption* is used.

Adsorption is essentially limited to the surface of the solid and should be distinguished from absorption which implies the penetration and the subsequent diffusion of the drug into the solid thickness. Two general adsorption processes can be considered: *physical adsorption* in which the adsorbed compound is bound to the surface through weak interactions such as van der Waals forces and *chemical adsorption* (chemisorption) which involves the stronger valence or ionic bonds. Adsorption is likely to occur with glass containers. The most important difference between adsorption and absorption is that adsorption is a saturable effect (in general monomolecular) and absorption is not. Therefore, the losses by adsorption are limited except for drugs at low concentration. The

adsorption phenomenon is generally described by Freundlich or Langmuir isotherms and occurs more frequently with drugs that have an aromatic nucleus. Adsorption is a rapid process and its extent is governed more by the total exposure surface and temperature than by the contact duration.

During the *absorption* process of a solute by the polymeric matrix constituting the walls of the device, the polymer could be considered as a lipophilic liquid with infinite viscosity. Therefore, absorption should be considered as dissolution of the drug into the polymeric phase and leading to equilibrium (partition coefficient). Thus, generally speaking, the more lipophilic a drug the more it is likely to be extracted from its solution by the polymer. The uptake of a drug by a polymer is strongly related to the polymer-water partition coefficient of the drug and to its octanol-water coefficient [3, 4]. The extent of drug absorption will depend mainly on its diffusion rate, residence time and exposure surface.

Loss of drugs by sorption is potentially clinically significant. Several studies have demonstrated losses of from 4% for hydrophilic drugs such as flucloxacillin sodium to 93% for more lipophilic chlorpromazine [5]. These losses strongly depend on the interaction surface, duration of exposure, pH and respective lipophilic properties of drug and



polymer. Drugs having demonstrated problems include isosorbide dinitrate, thiopental sodium, benzodiazepines and phenothiazines [5, 6].

Anticancer drugs have a very narrow therapeutic range and any loss by uptake by the administering device can cause reduction of the dose to a sub-therapeutic level, harming the patient therapy. For proteins and peptides, adsorption can be a serious problem becoming significant when they are present in low concentrations in solutions, for example the decapeptide derivative of LHRH [7]. This chemisorption of peptides onto glass is related to the bonding of their charged amino groups and silanol residues onto the glass surface at low pH. Thus, chemisorption is strongly dependent on the pH of the solution. The same has been observed with radiopharmaceuticals with significant losses of the administered activity for example with macro-aggregated albumin [8] stored in plastic syringes and varies considerably with the contact time (up to 83% for 12 hours) and with different brands of syringe (33-42%). The chemical nature of polymers is of paramount importance for their

emulsifying agents such as polysorbates. These emulsifying agents are used to obtain injectable micelle suspensions of poorly water-soluble compounds such as taxanes or to stabilise therapeutic proteins such as monoclonal antibodies. Among non-aqueous solvents ethanol, propylene glycol and PEG at concentrations up to 25% were unable to extract DEHP from PVC containers [14]. On the other hand polysorbate 80 was able to leach DEHP into the solution in contact with PVC bags. An additional problem is the not well-defined composition of polymers which can vary from one manufacturer to another, making it difficult to extrapolate from interaction studies.

The long-term toxic effects of DINPs are not clearly demonstrated and contamination of intravenous solutions by PVC plasticisers is not considered by the EU as a cause of internal exposure to consumers [15]. However, the precautionary principle implies it is not desirable to expose patients to these compounds, especially paediatric patients. Moreover, plasticiser can cause unexpected instability of drugs formulated in non-aqueous solutions. In Waugh's study, a taxol formulation

Anticancer drugs have a very narrow therapeutic range and any losses by uptake by the administering device can reduce the dose to a sub-therapeutic level.

capacity to absorb solute but also the brand or batch of the devices. Thus, even simple devices cannot be considered as equivalents from one particular brand to another.

The majority of studies concerning the compatibility of cytotoxic drug solutions with infusion bags and sets have investigated polyvinyl chloride (PVC) [9-11], but few have studied the drug sorption of other polymers which can be used to manufacture infusion sets such as low-density polyethylene [12, 13]. In all studies, PVC appeared to lead to the most sorption. Among the drugs tested only carmustine showed significant interactions with polymers. Carboplatin, cytarabine, 5-FU, gemcitabine, methotrexate, melphalan, dacarbazine and vinca alkaloids did not exhibit any sorption.

Leaching from packaging components

The second type of interaction is the migration of compounds from the polymer into the solution. These compounds are mainly plasticisers but metallic catalysers or stabilising agents can also be released. PVC may contain up to >40% of plasticisers mainly di-"isononyl" phthalates (DINPs) such as diethylhexyl phthalate (DEHP) which can migrate to the solution [14]. Since plasticisers are lipophilic their extraction from the polymer is favoured by lipophilic solutions such as non-aqueous solvents, lipid emulsions (liposomes) or solutions containing

consisting of 6 mg/mL paclitaxel in 50% polyoxyethylated castor oil and 50% dehydrated ethanol was added to glass bottles, PVC infusion bags or polyolefin containers containing 5% dextrose or 0.9% NaCl and stored for 12-24 hours at 20-23°C [16]. Solutions stored in PVC became hazier than solutions stored in glass or polyolefin containers. DEHP was found in solutions stored in PVC but not in solutions stored in glass or polyolefin. Thus, paclitaxel solutions should be stored in glass or polyolefin containers or delivered through a polyethylene-lined infusion set. This recommendation should be applied to other non-aqueous formulations of anticancer drugs such as etoposide, docetaxel and liposomal suspensions.

A totally unexplored field of research is the compatibility between plastics and therapeutic proteins such as monoclonal antibodies. Indeed, the stability of these proteins is a very complex problem. In particular, hydrophobic interactions between a protein solution and a surface can induce aggregation responsible for immunological side effects. Moreover, drug containers (plastic and glass) could release traces of metals which could catalyse oxidation reactions. Adsorption onto glass is also an important concern.

In conclusion, interactions between anticancer drugs and administration devices are an underestimated problem.

Fortunately, the vast majority of these drugs are not concerned. However, particular care should be taken for non-aqueous solutions. When interactions occur they can be very subtle and their extent can strongly depend on several factors related both to the drug solution and the delivering device. Thus, any modification of these parameters should be carefully checked by a pharmacist to ensure the quality of the drug finally administered to the patient.

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Contamination from handling cytotoxic agents

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Contamination of personnel who handle cytotoxics has been proved via traces in urine. Despite safety standards for handling cytotoxics, operators can still be exposed to them, mainly through skin contact. Identification of sources of contamination is recommended to improve working procedures.

Previous studies

Studies of contamination on vials, plungers of syringes, gloves, infusion bags, and work surfaces have been published.

Vials

Some authors have measured the amount of cytotoxic drug present on the outer wall of vials containing these agents, on receipt from the pharmaceutical supplier. A significant number of vials had a quantifiable level of external contamination (up to 2.5 ng of 5-FU per vial) [1-3].

Plungers of syringes

The contamination of the plungers of syringes used for handling cytotoxic drugs was measured [4]. The results showed that all the plungers were contaminated, amounts varying from 3.7 to 445.7 ng of cyclophosphamide.

Gloves

Gloves offer the first line of protection when handling cytotoxic drugs and are frequently in contact with these agents. A few studies showed that gloves used for biological safety cabinets (BSCs) were frequently (42–100%) contaminated during preparation of the drugs and cleaning of the hood [4, 5]. Favier et al. showed a contamination rate of 100% after only one dose was prepared. The amounts of cytotoxic agent detected were significant: Sessink et al. demonstrated up to 87 µg, and Favier et al. 180 µg [5, 6]. Because of the number of potential sources of contamination (drug preparation, vials, syringes, infusion bags, various surfaces), it is almost impossible to prevent contamination on the outside of gloves during normal work. Therefore changing gloves is recommended at least every 30 minutes. In addition, the quality of gloves must be carefully checked as shown by Wallemacq et al. [7].

Infusion bags

Infusion bags are an important source of contamination of gloves and environment. Studies carried out

on the external surface of bags prepared in a pharmacy have shown that they became contaminated with cytotoxic agents, independent of the equipment used for their preparation (isolators or BSCs) [8, 9]. Favier et al. [8] found measurable amounts of 5-FU on infusion bags varying from 70% to 100% for isolators, and 10% for BSCs.

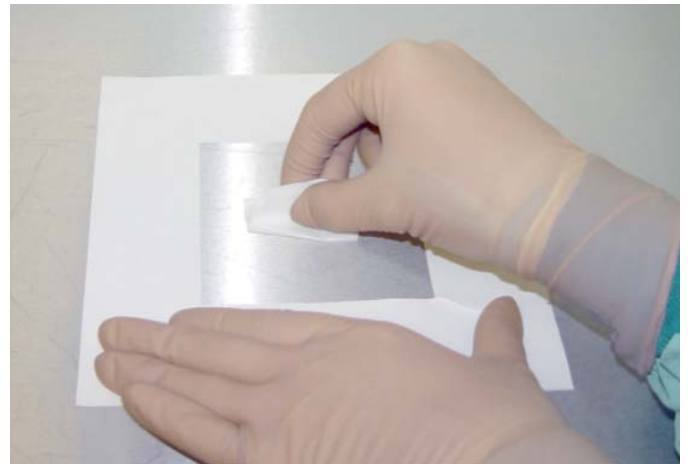
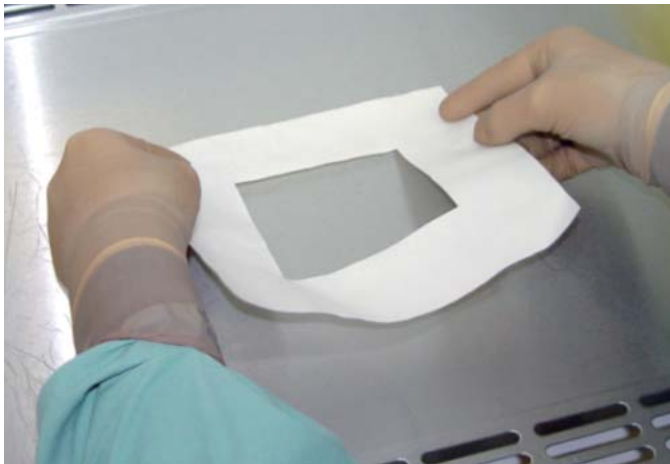
Work surfaces

In several publications, surface contamination with different cytotoxic drugs (mainly cyclophosphamide, ifosfamide, 5-FU and methotrexate) was estimated using a wipe sampling method [5, 8-10]. These studies were carried out on different surfaces, inside and outside the isolators and BSCs. The samples selected were potentially contaminated areas such as the work surface inside the isolator or the BSC, the floor in the preparation room, computers and furniture. Substantial levels of several antineoplastic agents were detected at various sites in drug preparation areas, whatever the equipment used. For example, Connor et al. indicated that 76% of the pharmacy samples were contaminated with measurable amounts of cytotoxic drugs.

Rhône Alpes studies

In 1999 we carried out a similar study in six French hospitals that perform between 3,500 and 26,500 preparations per year with the objective of determining the level of contamination with 5-FU of different cytotoxic drug preparation units, three using BSCs and three using isolators [8]. The main results were:

- A higher rate of contamination inside and outside isolators compared with BSCs, with measurable amounts of 5-FU detected in 79.2% (19/24) of the surface samples within isolators and 8.3% within BSCs (1/12). In the preparation rooms, 29.6% (8/27) of the surface samples outside isolators were found contaminated and no positive samples outside BSCs (0/29).
- 86.2% (25/29) of the samples collected on the outside of infusion bags prepared within isolators were contaminated but only 3.3% within BSCs (1/30).



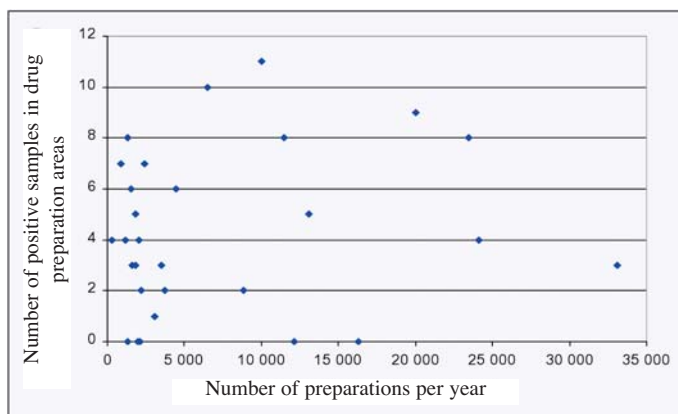
In 2007, we carried out a larger study in 30 hospitals of the French Rhône Alpes region that are monitored by the ONCORA cytotoxics laboratory. The aims of this study were to measure the contamination with 5-FU at various hospital sites (including the drug preparation and administration areas), to observe practices during the preparation of cytotoxic drugs and to make a comparison with the 1999 study.

The sampling locations were selected as potential areas of contamination on the basis of the results of previous studies. In each cytotoxic drug preparation unit, at least two samples were collected on the work surface within BSCs or isolators (one before cleaning and one after in order to evaluate the effectiveness of the decontamination procedures). Four more samples were also taken: two samples on the outer operators' gloves and two on the outside of infusion bags. In addition, it was possible to get samples in some outpatient clinics. Samples from objects and surfaces were performed with moistened filters wiping calibrated surfaces when possible (for gloves and infusion bags, immersion in distilled water was used) see Figure 1. The preparation of cytotoxic drugs was centralised under the control of a pharmacist in 24 hospitals, 16 using BSCs and eight using isolators. It was under the responsibility of nurses

in the last six hospitals, all equipped with BSCs. The number of doses prepared ranged from 325 to more than 33,000 per year. The preliminary results on the 555 collected samples were:

- Measurable amounts of 5-FU were detected in 28% of the samples collected in preparation areas and 23% in the administration areas.
- A high rate of contamination of the outer preparation gloves (more than 60%) and a 20% rate of contamination of infusion bags were found. Some gloves were heavily contaminated.
- The level of contamination in the immediate preparation areas did not correlate significantly with the number of doses of chemotherapy prepared per year (Figure 2). This confirms the importance of establishing strict working procedures under the control of a pharmacist.
- If we compare the results of the first two groups of hospitals performing preparation under the control of a pharmacist with BSCs or with isolators to those of the preliminary study, we still find a difference in terms of contamination between the two techniques, but with a smaller gap, suggesting that operating procedures have been improved.
- In the areas where the drugs are administered, many samples taken on nurses' gloves after they had connected or disconnected infusion bags were found to be contaminated. 5-FU was detected in nearly half of the samples, but the number of samples collected was a little bit too low (only 18 samples collected): these preliminary results need to be confirmed by a larger study of contamination at the time of administration.

Figure 2: Contamination does not correlate with number of doses prepared



Conclusion

Contamination studies show that occupational exposure of workers handling cytotoxic agents can be controlled only if all the possible sources of contamination are identified and if suitable systems of protection are used. The validation of work procedures should include surface analysis of critical points such as gloves and various surfaces in pharmacies and wards. In addition, initial and continuing education of technicians, pharmacists and nurses is highly recommended to obtain as low a level as possible of cytotoxic contamination.

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Medical devices for the safe reconstitution of cytotoxics

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The main objectives of these devices are to protect patients against bacterial contamination and healthcare workers against chronic exposure to chemical contamination. Many manufacturers have developed medical devices for the safe reconstitution of cytotoxics.

For many years, the use of chemotherapy has been growing considerably. Because of the increase in this activity and the risk incurred by healthcare workers when handling cytotoxic drugs, safety devices have been developed to improve quality in the preparation of these drugs. Pharmacy technicians also require training.

Selection criteria for medical devices

Limitation of contamination

The imperative to limit both microbial and chemical contamination has led to the adoption of closed systems. According to the American Society of Health-System Pharmacists (ASHP), *closed-system drug-transfer devices mechanically prevent the transfer of environmental contaminants into the system and the escape of drug or vapour out of the system* [1]. This echoes the definition adopted by the National Institute for Occupational Safety and Health (NIOSH) [2]. This definition, taking into account drug vapour, clearly indicates that air-venting devices, even those with a 0.20 µm filter membrane, are not strictly closed-system devices. The recommendations of the GERPAC-Europharmat workgroup (the French isolators users' group - Les Journées Nationales d'Etudes sur les Dispositifs

Médicaux) based their definition on that of the ASHP, but specified that closed systems should protect the operator against the escape of vapour, liquids and solids [3]. Compliance with these recommendations cannot be considered a substitute for ventilated cabinets or isolators.

Avoidance of needle risks

Avoiding the use of needles achieves several goals. Needles increase the risk of operator exposure to cytotoxic drugs by contact or injection. Moreover, the absence of a needle is a good way to decrease contact with liquid aerosols. These are caused by drug droplets squirting out, when the needle is withdrawn from the vial, if overpressure has been caused during manipulation. For these reasons, ASHP, GERPAC and Europharmat recommend needle-less systems if possible. Unfortunately, the use of air-venting systems is not always possible, e.g. if the vial opening is too small, or for soap solutions. Needles are necessary in such cases. A needle safety transfer device may protect operators against the risk of puncture, but does not decrease the risk of aerosol formation.

Container-contents interactions

It is important to take into account the possible

Figure 1: BD Blunt safety transfer device (BD Medical)



Figure 2: PCHIMX-1 (DORAN International)



Figure 3: Tevadaptor (Teva)



physico-chemical interactions between anticancer drugs and the device. In particular, devices containing plasticisers such as PVC should be avoided as much as possible [4-6]. It is then preferable to use devices made of polyolefins (polyethylene, polypropylene) or polyurethane. In addition, chemical contaminants from the surroundings cross the wall of a device (permeation). It can occur during sterilisation with peracetic acid [7] or hydrogen peroxide. Permeation through medical devices is a potential toxic risk to the patient and the loss of stability of the drug may be revealed by a pH change.

Classification of devices

The latest International Society of Oncology Pharmacy Practitioners (ISOPP) standards [8] classify special devices for the reconstitution and administration of cytotoxic drugs as follows:

- (1) Devices to protect the handler of the vial/ ampoule
- (2) Devices to protect the operator during preparation
- (3) Devices to protect the administrator during administration of the cytotoxic drug to the patient.

Devices/systems used to transfer the drug solution from a vial to an infusion bag fall in class 2. ISOPP standards specify that manufacturers have to indicate if the device can be used for the entire or only a part of the preparation process, if the device can be used if more than one vial is necessary for a preparation, and if studies demonstrate the ability of the device to reduce or eliminate environmental contamination.

Class 2 devices may be divided into two groups, based on their function: devices to access the primary vial (access and reconstitution devices) and devices to access the infusion bag (dilution devices). For the reconstitution devices, four points have to be strictly controlled: limitation of aerosol formation, asepsis, safe use and the residual volume. For dilution devices, we have to be vigilant on the universality of use, maintenance of asepsis, safe use and minimal chemical contamination.

Access and reconstitution devices [9]

If a needle is required, a safety transfer needle can be used to decrease the risk of needlestick. The Blunt Fill needle (Figure 1) has a special bevel (45° angle). This bevel is sufficient to penetrate the cap, but ten times the force is needed to puncture the skin or the operator's gloves. Nevertheless, the risk of an aerosol is not reduced.

Spikes are widely used to access the vial. The syringe connection to the spike must be the Luer-lock type for safety. Important criteria include the type of connection (bidirectional valve or not), a single or double channel, the residual volume, or pore size of the air filter (0.45 or 0.20 μm). The double channel spikes (Baxter's Chemo-Aide Pin, Codan's Spike, Hospira's CS-51 Spike, B.Braun's Chemo-Spike) incorporate an air vent protected with a 0.22 μm hydrophobic filter. B.Braun's Mini-spike has a 0.45 μm hydrophobic air filter. Hospira's CS-53 spike only has one channel.

Dilution devices

Dilution devices allow access to the bag contents. The selection criteria for these devices are the polymer used for manufacture, a bidirectional valve to allow needle-free operation, a Luer-lock connection, and the residual volume.

Chemo-set and Connect-Z are two extension sets. They are used with special infusion devices to which they are connected by a bidirectional valve, allowing needle-free manipulation. The Luer lock between the extension set and the infusion set ensures safe transfer of the anticancer drug solution. PCHIMX-1 (Figure 2) is a recent special extension set. It is a device with two independent entrances made to be connected to two infusion bags. Like the other devices, it allows safe handling because it has a bidirectional valve on the tube that is connected to the cytotoxic drug infusion bag.

Devices called in practice "closed systems"

The Tevadaptor (Figure 3) is a three-part device including a vial adapter, a syringe adapter and an infusion bag adapter. The vial adapter fixes firmly to the vial. It has a dual channel perforator with a hydrophobic 0.22 μm air-filter. The infusion bag adapter contains a perforator with two channels: one for the injection of the cytotoxic drug solution and another for the administration. The syringe adapter allows the transfer of the solution from the vial to the infusion bag using a Luer connection to reinforce safety. Nevertheless, the Tevadaptor cannot be considered, or recommended, as a closed-system device.

PhaSeal from Carmel is the only closed-system device suitable for handling cytotoxic drugs. It allows the drug to be transferred from the vial to the syringe and then to the infusion bag without

any contact between the drug and the environment at any time.

This multi-component system uses a double membrane to enclose a specially cut injection cannula as it moves into a drug vial, Luer-lock, or infusion-set connector. Several studies comparing PhaSeal to traditional techniques show a significant reduction in environmental contamination if this device is used [10, 11].

Conclusion

Cytotoxics can be safely reconstituted if aseptic handling is strictly respected and chemical contamination is minimised. Devices decrease the risk of chemical contamination and maintain a good level of asepsis. However, these devices must be used in a clean environment and operators must wear protective clothing and must be regularly trained and evaluated.

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OECD FACTS

Doctors' and nurses' pay in OECD countries

Given that labour cost is an important component of total health expenditure, variations in remuneration levels can provide some insights into cross-country variations in health spending. Comparative data on remuneration levels may also help national authorities to identify benchmarks for fee and salary negotiation purposes. In addition, information on remuneration levels may be useful in understanding the migration of health professionals across countries.

The graph shows physicians' remuneration expressed in terms of the gross average income in each country, e.g. 3.0 means three times the average income, before social security and tax deductions. These salaries may be underestimated due to additional payments for over-time or weekend work, the whole income not being stated, informal payments in some countries and self reporting of the income.

Physicians' remuneration, specialists and general practitioners, OECD countries, 2005



(1) Data for self-employed specialists and GPs in Belgium include practice expenses resulting in an over-estimation.
 (2) Remuneration of salaried specialists in Greece is for 2005 while it relates to 2004 for self-employed specialists.
 (3) Given that GDP per capita overstates the average income, gross national income (GNI) is used for Ireland and Luxembourg.
 For more information, see the Sources and Methods at: www.ecosante.org/OCDEENG/260000.html
 Source: OECD Health Data 2007.

Specialists' remuneration is high in the Netherlands and the US and relatively low in Czech Republic, Norway and Hungary. A relatively small number of specialists correlates with high income although other factors also affect income.

Regarding nurses, based on data from 16 countries, the relative income of hospital nurses is on average 1.2 times per capita GDP. Remuneration relative to the average national income is highest in Portugal, followed by the US and Australia. It is lower than the average income in Czech Republic, Hungary and Norway.

Extravasation - how to avoid, how to treat

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Extravasation does not occur very often but its consequences can be severe and painful. Every ward dealing with cytotoxics should have an extravasation kit and all staff should be trained in administration and extravasation procedures.

Introduction

Many cytotoxic agents are administered intravenously and when given correctly they cause few side effects at the injection site. However, when they are injected or leak into the surrounding tissues, a reaction varying from irritation to necrosis may arise. Extravasation occurs in 0.1% to 6% of adults treated with chemotherapy. The severity of tissue injury depends on the type and concentration of the chemotherapeutic agent and the quantity injected.

Cytotoxic agents may be classified as irritants or vesicants. Irritants cause an inflammatory reac-

tion with aching, swelling, pain or phlebitis at the injection site or along the vein; sclerosis and hyperpigmentation along the vein; and burning, local warmth, discomfort, erythema or tenderness. These symptoms are self-limiting and have no long-term impact.

Vesicants (Table 1) cause severe and lasting tissue injury and necrosis. Symptoms may arise immediately after extravasation or appear after several days or weeks. Patients complain of pain or local burning at the infusion site, mild erythema, itching or swelling. Over time, the symptoms of erythema and pain may increase and a discoloration

Table 1: Vesicants and guidelines for antidote use

Drug	Antidote	Advice
Amsacrine Anthracyclines (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin)	No specific antidote DMSO Dexrazoxane	Apply locally as soon as possible and repeat every 8 hours for 7 days. • 1000 mg/m ² IV within 5 hours of extravasation on day 1, 1000 mg/m ² on day 2, 500 mg/m ² on day 3 • Ice packs
Carmustine Dactinomycin Melphalan Mitomycin C	No specific antidote No specific antidote No specific antidote DMSO	Apply locally as soon as possible and repeat every 8 hours for 7 days.
Nitrogen mustard (Mechlorethamine)	Sodium thiosulfate	2 mL of a solution of 4 mL sodium thiosulfate + 6 mL sterile water for injection SC
Streptozotocin	No specific antidote	
Taxanes (Docetaxel, Paclitaxel)	No specific antidote	
Vinca alkaloids (Vinblastine, Vincristine, Vinorelbine)	Hyaluronidase	150-1500 u SC Hot packs
Vindesine	Hyaluronidase	150-1500 u SC

DMSO: dimethylsulfoxide; IV: intravenous; SC: subcutaneous

and induration of the skin, dry desquamation or blistering may develop. In case of a significant extravasation, necrosis, eschar formation or ulceration with involvement with the underlying tissues may occur. The indolent ulceration lacks granulation tissue formation and does not heal.

Prevention of extravasation

Prevention is the most important issue in extravasation. Therefore certain rules should be respected:

- In all departments where cytotoxic agents are given, written guidelines for handling cytotoxic agents and procedures in case of extravasation should be present.
- An extravasation kit with instructions and all the necessary materials and medication to treat an extravasation should be available (Table 2). There should be a form to report the extravasation to the authorities (hospital direction, legal department, nursing department).
- Persons responsible for administering cytotoxic drugs should be informed and trained in medication use; the problems that may arise in case of extravasation and the procedures to adhere to.
- The placement of a subcutaneous device before starting chemotherapy is recommended for vesicant drugs and for infusions of longer duration, e.g. infusions lasting more than one hour. However, a subcutaneous device does not eliminate the possibility of extravasation and the same recommen-

dations apply as for administration of medication by a peripheral vein.

- A cytotoxic agent should not be administered in an extremity if in the previous 48 hours a venopuncture was performed above the place of catheter insertion.
- Medication should never be administered with a butterfly needle and even in the case of a bolus injection or a short infusion, a catheter has to be inserted into the vein. Small and fragile veins should be avoided. The catheter should never be inserted in a limb that is affected by lymph edema or neurological symptoms. Veins adjacent to tendons, nerves or arteries should be avoided, while areas of high venous pressure should not be used.
- The placement of the catheter should be in the forearm and not on the hand. If extravasation were to happen, the tissues and muscles in the forearm might prevent involvement of ligaments, nerves and bone.
- Before administering a cytotoxic agent, the catheter should be flushed by a free flowing infusion with saline 0.9% or glucose 5% solution for at least five minutes. At the end of the administration, the same procedure is repeated.
- The patient should be informed that in case of pain or other discomfort the nurse must be informed immediately.
- The exact position of the catheter should be checked by aspiration of blood. And the medication should be administered slowly.

Table 2: Contents of an extravasation kit

Materials		Amount
Syringes	3 mL	5
	5 mL	5
	10 mL	5
Needles	19 gauge	10
	27 gauge	10
Sterile gauze dressing	10 cm x 10 cm	5 packets of 5
Alcohol swabs		1 packet
Disinfecting sponge		4
Waste disposal bag		1
Dexrazoxane		10 x 500 mg
Hyaluronidase ampoule	1500 IE	2
Sodium thiosulphate ampoule 20%	5 mL	2
Dimethylsulfoxide	100%	100 mL
Sterile water	10 mL	4
Saline 0.9%	10 mL	4
Extravasation report form		4
Insurance document		2
Cytostatic drug compendium		1
Dated extravasation protocol/antidote monograph		1
Cold pack in freezer		1

Treatment of extravasation

If extravasation is suspected either because the patient complains or because of local signs, the administration must be stopped, the nurse must aspirate as much as possible of the injected medication, leave the catheter in place and call for a physician. The physician will give instructions how to deal with the event and may initiate treatment for extravasation. The event and the treatment procedure must be noted in the patient's file and on the extravasation form.

The type of treatment for extravasation depends on the medication:

Irritant medication

- The catheter is removed and the affected limb is elevated.
- Cold or warm compresses are applied. Hot packs cause vasodilatation and lead to the dilution of the medication. Cold packs cause venous constriction and lead to localisation of the medication, which may increase degradation of toxic metabolites. They may also reduce local inflammation and pain.
- Inflammation may be treated with local anti-inflammatory drugs. Pain should be treated with analgesics.

Vesicant medication

- The catheter is left in place.
- The vesicant may be diluted by injecting the subcutaneous tissues with 0.9% saline. Cannulas inserted by small inci-

sions allow saline to infiltrate and flush out the vesicant.

- An antidote may be administered (Table 1).
- The affected extremity is kept elevated and a cold or hot pack (vinca alkaloids) is applied.
- If ulceration develops, immediate or delayed surgical debridement with delayed closure is indicated.

Conclusion

Extravasation is a severe complication of chemotherapy. Prevention by appropriate guidelines for chemotherapy administration and training of nurses is of utmost importance. In the event of extravasation, the correct treatment should be given according to the drug involved.

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Ambulatory devices for prolonged infusion of cancer chemotherapy

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One of the key factors in the success or failure of ambulatory chemotherapy is the selection of the ambulatory infusion device. As new devices have entered the market in recent years, the selection process becomes increasingly complex.

For many years it has been recognised that administration of some antineoplastic drugs in prolonged, continuous infusions, as opposed to traditional short infusions or bolus injections, can improve therapeutic response and modify drug-related toxicity [1, 2]. These clinical developments have been combined with technological advances in small, portable infusion devices to enable patients to receive ambulatory chemotherapy by continuous infusion in the community setting [3]. Ambulatory infusion devices may be classified by four main groups (Table 1), although other types of device are available.

Device selection

Many factors influence the selection of infusion devices. These include the volume to be infused, rate of infusion, duration of infusion, accuracy required, patient protection and alarm systems required, patient acceptability (ease of use, size, weight, noise level) and the budget available for both capital and consumable costs. Additional device-specific issues also need to be taken into account, including maintenance and testing costs (electronic devices), and the time taken for pharmacy aseptic units to fill device reservoirs, which can vary considerably between devices.

There is no single device suitable for all applications, and the reader is referred to the specialist literature for a discussion of the key attributes required and evaluation of different devices [4, 5].

A detailed discussion of individual infusion devices is beyond the scope of this short article, but some general guidance on the advantages and disadvantages of the main device categories listed in Table 1 is provided to aid in the selection process [6].

Syringe drivers (example Graseby MS26)

Advantages: Syringe drivers are small, lightweight devices and the range of flow rates achievable (0.06 – 41 mL/hour for Graseby MS26) makes them ideal for continuous infusion of chemotherapy. These devices use standard Luer lock syringes as the infusion reservoir which significantly reduces consumable costs. Although the flow is pulsatile, the long term accuracy of syringe drivers is usually good. A “Lockbox” is available with some devices to secure the pump and prevent tampering. Capital purchase costs are modest.

Disadvantages: The flow rate of the Graseby MS26 and MS16A syringe drivers is set according to the length of syringe plunger travel (in mm) over a fixed time period. Setting the flow rate in

Table 1: Classification of the main groups of ambulatory infusion pumps

Classification	Description	Examples (manufacturer)
Syringe driver	Uses standard Luer lock syringe (up to 20 mL volume) as drug reservoir, and battery – driven motor to “drive” syringe plunger and infuse drug. The volume delivered over 24 hours can be adjusted within limits. Syringe is disposable, single use.	Graseby MS-26 and MS-16A
Elastomeric pump	An elastomeric balloon reservoir is filled with drug solution and the elastic properties drive the drug out through a flow restriction device at a constant flow rate. The reservoir may be contained in a rigid protective outer casing. Entire device is disposable, single use.	LV Infusor and SV Infusor (Baxter Healthcare)
Mechanical pump	Uses a spring mechanism which applies pressure to a PVC drug reservoir contained in a rigid casing. This forces the drug solution through a flow restrictor at a constant rate. A variety of different flow rates and reservoir volumes are available. Reservoir is disposable, single use.	Paragon Infuser (I-Flow Corporation)
Electronic device	Battery powered, usually based on a peristaltic mechanism, featuring an integrated reservoir/cannula which is disposable and normally constructed from PVC. These devices can be very sophisticated with various alarms, programmable flow rates and, in some cases, the capability to download infusion history.	Walkmed 350 (McKinley Medical) CADD-Prizm VIP (Graseby)

mL/hour requires a calculation involving syringe length and volume. Confusion between the two Graseby devices can occur because the MS16A device delivers the set travel over one hour, whereas the MS26 delivers the set travel over 24 hours. The alarm and safety systems on these devices are relatively basic, require routine maintenance and are not easy to clean if contaminated with cytotoxic drug infusion. The small reservoir size (syringe) requires frequent changes during long-term infusions.

Elastomeric pumps (example Baxter LV infusor)

Advantages: Light and compact because elastomeric pumps have no battery or motor. No capital costs, the devices are disposable, single use consumables. A wide range of reservoir volumes and flow rates is available (240-272 mL and 1.5, 2, 5, 7, 10 mL/hour, respectively for Baxter LV infusor), and some devices with multiple infusion rates are now available. Most devices include an in-line particulate filter and some also include an air-bubble elimination filter. Accuracy is typically claimed as +/- 10-15%, which is acceptable for most chemotherapy applications. In some devices, the infusion reservoir is protected by a rigid plastic casing. Operation of elastomeric devices is silent.

Disadvantages: Consumable costs are relatively high for these disposable, single-use devices, which can, over a period of time, cost more than the one-off capital purchase and consumable purchases (reservoirs and batteries) associated with electronic devices. Flow rate is influenced by temperature (increase in temperature results in increased flow rate), height of device relative to infusion site, and viscosity of the infusion

(confusingly, some devices are calibrated using 5% glucose infusion, others using 0.9% sodium chloride).

Mechanical pumps (example Paragon I-Flow)

Advantages: No motor or electronic components, so no batteries required. Drive mechanism (casing and spring mechanism) is designed for multiple use, so that the infusion reservoir is the only consumable which reduces operating costs compared to elastomeric devices. Nominal reservoir volume is 100 mL with a range of fixed flow rates available from 0.5 to 100 mL/hour. The Paragon Select-A-Flow is available in three variants, so the flow rate can be selected from 0.5-3.5, 1-7, and 2-14 mL/hour in increments of 0.5, 1.0 and 2.0 mL/hour, respectively. The claimed accuracy varies between +/- 10-15%, depending on flow rate, and this is adequate for most chemotherapy regimens. Most spring-powered devices include both particulate and air filters in line. Some devices are fitted with indicators to monitor infusion progress.

Disadvantages: One of the main issues is the weight of mechanical pumps. For example, the unfilled weight of the Paragon device is 260 g, compared to 40-65 g for elastomeric devices. As with elastomeric devices, operating temperature, infusion viscosity and the height of the pump relative to the infusion site can all influence flow rate and infusion accuracy. The non-disposable components can be difficult to clean in the event of a cytotoxic spillage.

Electronic pumps (example Walkmed 350)

Advantages: These versatile and sophisticated pumps offer a

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wide range of infusion reservoir volumes (typically 50-250 mL) and flow rate range (typically 0.1-20 mL/hour at 0.1 mL/hour increments). Accuracy is typically +/- 5%, and battery capacity allows between 450 and 650 mL to be delivered between battery changes. Most pumps are easy to programme and have either a coded lockout facility or a lockable pump case to prevent tampering. Usually there is an LCD panel providing programme and infusion status. Alarm and safety features are specific to individual devices, but typically include occlusion, air in line, low battery, pump malfunction indicators and systems to prevent the use of non-compatible administration sets. Some devices enable the infusion history to be downloaded to a PC and printed, and others may be programmed with different flow rates over a 24-hour period to facilitate chronotherapy.

Disadvantages: The capital cost of electronic pumps can be very high, and the consumable budget must include provision for batteries and regular maintenance, in addition to infusion reservoirs. However, one reservoir may contain several days' treatment, so overall consumable costs may be favourable. The more sophisticated devices can be bulky and, including the battery, the weight of the unfilled device can range from 350 g upwards. Calculation of battery life and training the patient to replace batteries is a further complication.

Pharmaceutical issues

Pharmaceutical issues to be considered include the filling of the device and infusion-container compatibility and stability

issues. Syringe drivers, electronic and mechanical pumps offer the advantage that there is no backpressure during filling. The operating pressure of some elastomeric devices can exceed 500 mmHg, and this must be overcome when filling and inflating the elastomeric reservoir. These issues are of particular significance when large batches are involved causing operators repetitive strain injury and, if automated filling systems are used, the risk of equipment damage. Filling cytotoxic infusions against a backpressure may also increase the risk of aerosol formation and occupational exposure.

Infusion devices should be biocompatible, e.g. ISO 10993-1 compliant, and must also be compatible with the drug infusions they are used to administer. This latter issue is covered in another article, see page 20, *Compatibility of anticancer drug solutions with administering devices*, by Professor Alain Astier.

The physical and chemical stability of drug infusions in ambulatory devices during storage prior to use, and under in-use conditions, is critical. Device manufacturers can often provide this information and stability reports for specific drug-device combinations are available in the literature [7, 8]. Since ambulatory infusions may be exposed to prolonged refrigerated storage (2-8°C) followed by in-use temperatures of up to 37°C, studies based on the "sequential temperature" design [9] provide the most rigorous validation of stability.

In conclusion, prolonged infusion chemotherapy presents many challenges across the clinical, scientific and technical sectors of pharmacy.



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