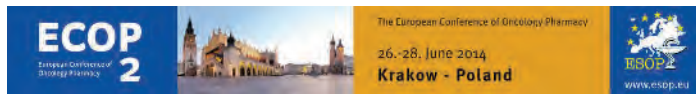


If one gives an answer before he hears, it is his folly and shame 3



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EJOP is published quarterly and distributed to more than 3,000 oncology pharmacists, pharmacy technicians and subscribers in 33 countries and at major international and national conferences. EJOP is available online (www.ejop.eu).

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ISSN EJOP: 1783-3914

Print Run: 3,000 Printed by PPS sa



Published in Belgium
by Pharma Publishing &
Media Europe
copyright@ppme.eu

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Subscription Rates 2013:

	Europe	Non-Europe
Individual:	€170	€200
Hospital/University:	€330	€360
Corporate:	€420	€450
Student:	€130	€160

Individual and student subscriptions are subject to 21% VAT Belgian Government tax.

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Change of address notices: both subscriber's old and new addresses should be sent to marketing@ppme.eu at least one month in advance.

Claims: when claims for undelivered or damaged issues are made within four months of publication of the issue, a complimentary replacement issue will be provided.

If one gives an answer before he hears, it is his folly and shame

Proverb 18:13

We know about our responsibilities. We have heard the request for patient support. But has anyone else?

Every second man and every third woman is diagnosed with cancer during their lifetime. About one-half of people with cancer are to be cured after five years. Nevertheless, cancer is the second most common cause of death overall, after deaths caused by cardiovascular failure. With few exceptions, the incidence of cancer increases sharply with age, and so ageing is the most important (and unfortunately unchangeable) risk factor for cancer. In addition to epigenetic changes that increase over the life course, other factors play a role. These include weakening of the primary defences against cancer by the immune system and DNA repair machinery.

Improved survival rates can be achieved by improving therapeutic approaches to cancer care. The chronicity of the disease makes the additional support provided by pharmacists indispensable.

Thousands of epidemiological studies, in conjunction with clinical trials and basic research, produce an important overall picture of cancer prevention. We agree that at least 50% of all tumours could be prevented through following a healthy lifestyle. The main risk factors are cigarette smoking, poor nutrition, obesity, and physical inactivity. Preventative interventions include smoking cessation, sun protection, plant food, exercise, aspirin, human papilloma virus vaccination, and screening.

It is important that, for each tumour entity, different risk and preventive factors apply, and therefore the data must be interpreted accurately so that recommendations can be made. ESOP is supporting a call for action titled 'Stop cancer now!' This call for action was announced on World Cancer Day by the World Oncology Forum, which was organized by the European School of Oncology in partnership with *The Lancet*. The 'Stop cancer now!' appeal was also advertised in the *International Herald Tribune*, *Le Monde*, *El País*, *La Repubblica* and *Neue Zürcher Zeitung*, and also published alongside a commentary in *The Lancet* and in an article in *Cancer World*. The goal is to appeal to governments across the world to take action now to turn back the tide of cancer.

This year, the 17th European CanCer Organisation (ECCO) Congress will be held on 26 September–1 October 2013,



Klaus Meier
Editor-in-Chief



Amsterdam, The Netherlands. All society members have been working towards the 'Stop cancer now!' vision by integrating expertise and insights of the different professions and stakeholders in the oncology community to achieve the best possible outcomes for patients.

Professor Cornelis van der Velde, in his First President's Page for 2013, stated that 'I also believe that a sense of renewed focus and vigour is being felt throughout the wider oncology community this year'; 'We at ECCO believe that we are in a unique position to achieve this, as the only multidisciplinary and multi-professional organisation that connects and responds to all stakeholders in

oncology Europe-wide.'

Despite the shared understanding and objectives of all members of local and national healthcare teams, efforts towards good patient care are being thwarted by the shortage of drugs. This is evident in most important drug groups, but especially in cancer treatment. Nearly four months ago, we were faced with a worldwide shortage of one single drug, mostly used in protocols for colon cancer. As this drug could not be delivered for several weeks, pharmacy stock dwindled and, in some cases, ran out. Political pressure had to be brought to bear on pharmaceutical companies. About a year ago, President Obama opened serious discussions in the US about the responsibility of pharmaceutical companies to look after shareholder value, but not at the expense of patients, as exemplified by the plight of 170,000 or so new colon cancer patients in Germany.

The combination of globalization within the pharmaceutical industry, the scaling down of plant operations, the liberalization of drug selling, and the increased demand for quality has driven us to this critical point. As a result of safety concerns, and the cost and availability of life-saving treatments, EMA subsequently published a reflection paper on medicinal product supply shortages caused by manufacturing and the problems in good manufacturing practice compliance [1].

A survey conducted in 2011 by the Institute for Safe Medication Practices showed that 25% of clinicians indicated that an error had occurred at their site because of drug shortages [2]. Many of these errors were attributed to inexperience with alternative products.

EMA is aware that the crises in public health is caused by shortages of medicinal products, and believe that the

following actions are required: centralized assessment by multidisciplinary teams from within the pharmacovigilance network; the engagement of all stakeholders in the network; frequent engagement of experts inter-linked with, but not operating within the network; rapid and sophisticated communication of appropriate risk-management measures; and an implementation that is customized to the national situation.

In this issue of EJOP, we show again how ESOP provides professionals with state-of-the-art educational and scientific information by presenting cutting-edge clinical and pharmaceutical research. ESOP offers a variety of educational programmes to give young oncology pharmacists the opportunities to strengthen their skills, knowledge, and expertise,

while providing a platform for networking with other oncology pharmacists and relevant professionals in the field.

Nobody can tell that we have not heard and we are willing to share. Just do it!

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ECOP
European Conference of
Oncology Pharmacy **2**

26.-28. June 2014
Krakow - Poland

www.esop.eu



How can we improve safe handling of antineoplastic drugs: can devices be helpful

Safe handling procedures should be implemented in all areas where antineoplastic drugs are delivered, stored, prepared, administered, and disposed of in order to reduce contamination in the workplace and the resulting exposure to healthcare workers. Developing devices for the whole handling procedure must be addressed.

Hospital personnel are increasingly aware of the risks associated with occupational exposure to antineoplastic drugs, both during the preparation and administration of these hazardous agents. However, numerous studies confirm that, despite having developed standard safety procedures, contamination still occurs in practically all facilities where antineoplastic drugs are handled [1-6].

Thus, with today's rapid expansion of chemotherapy services, all efforts to minimize potential risks of exposure to these drugs are taken into consideration.

When considering safe handling of antineoplastic agents, all stages of chemotherapy production must be taken into account as an inseparable chain: from delivery of the drugs to preparation areas, to their reconstitution, through to their delivery to oncology departments, administration to patients and, finally, to their disposal after application. Alongside this, there is a risk that these hazardous agents can be released into the environment leading to exposure of workers.

When antineoplastic drugs are delivered, safety procedures can be optimized by using the correct labelling for transporting hazardous products. ESOP provides a tool to facilitate this: the 'yellow hand' label. This symbol indicates the hazard with a warning to all people who could come into contact with cytotoxic drugs during their transportation; it is designed to be easily understood even by an untrained person.

Preparation of antineoplastic drugs is a complex process. Numerous studies have shown that aseptic manipulation using the classical syringe and needle technique almost always results in contamination [7]. Therefore, every possible way of preventing workplace contamination with cytotoxic drugs should be considered. One of the best strategies to achieve this is to prevent the hazardous products escaping into the environment. For this purpose, special devices designed for safe handling of antineoplastic drugs can be helpful.



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Over the last ten years, medical devices for reconstitution and administration of antineoplastic drugs have been developed and improved upon. They have developed from classical needles and syringes, to early spikes with filters, to vented spikes with closed connections, and finally to the new era of devices called 'closed systems'. At present, pharmaceutical companies promote

various special devices designed for the reconstitution and administration of hazardous drugs. The main purpose of these devices is to support safe handling of the drugs by keeping the hazard inside the device, preventing or minimizing any possible contamination. Most of these devices are widely used by pharmacists and other healthcare workers in daily practice. In addition, closed system devices are gaining in popularity.

There are numerous published studies concerning the evaluation of devices for hazardous drug handling [8-13]. However, most of these studies are focused on assessment of devices designed for drug preparation. Thus, it is necessary to evaluate devices in terms of their efficiency at every stage of chemotherapy production.

In a recent study, we have assessed environmental contamination and occupational exposure to antineoplastic drugs in the pharmacy and oncology ward before and after implementation of the closed system drug transfer device (CSTD).

Environmental contamination with cyclophosphamide (CP) and 5FU was assessed by taking wipe samples from several surfaces in the areas where antineoplastic drugs are prepared (pharmacy) and administered (chemotherapy ward). To establish occupational exposure, the excretion of CP was measured in the urine of pharmacists and nurses handling cytotoxic drugs, including CP. In addition, we also assessed the exposure of doctors who were not directly engaged in the preparation or to administration of these hazardous agents. In the study, eight hospital workers were involved—two pharmacists, four nurses and two doctors. One pharmacist prepared antineoplastic drugs while the other pharmacist assisted. All four nurses on the chemotherapy ward were engaged in the

administration of the drugs. Two doctors did not handle the drugs but they had contact with treated patients.

Wipe and urine sampling were performed two times. The first time concerns monitoring of contamination and exposure during traditional preparation and administration procedures commonly used for many years. The second time concerns monitoring of contamination and exposure six months after the implementation of the CSTD.

Before implementation of the CSTD, the results show total spread of contamination with 5FU and CP in the nursing department, but also with CP in the pharmacy. Levels of contamination were higher for 5FU compared to CP, especially in the nursing department. The results of the wipe samples are presented in Table 1.

Before implementation of the CSTD the results show exposure to CP of all pharmacists and doctors and almost all nurses. From 62 urine samples collected over 24 hr, CP was detected in 31 urine samples (50%) concerning two pharmacists, two doctors and three nurses. The total amount of CP excreted per worker ranged from 106 to 500 ng/24 hr, see Figure 1. The mean amount of CP excreted per worker on group basis was 234 ng/24 hr (doctors: 343 ng/24 hr, pharmacists: 239 ng/24 hr, nurses: 177 ng/24 hr). The highest amount of CP excreted was found for one doctor (500 ng/24 hr) and for one nurse (492 ng/24 hr). The amount of CP excreted in urine from the pharmacist who assisted in preparation (358 ng/24 hr) was higher than from the pharmacist who prepared the chemotherapy infusions (120 ng/24 hr). These results show that workers who were not directly involved in the preparation and administration of antineoplastic drugs were the most highly exposed ones.

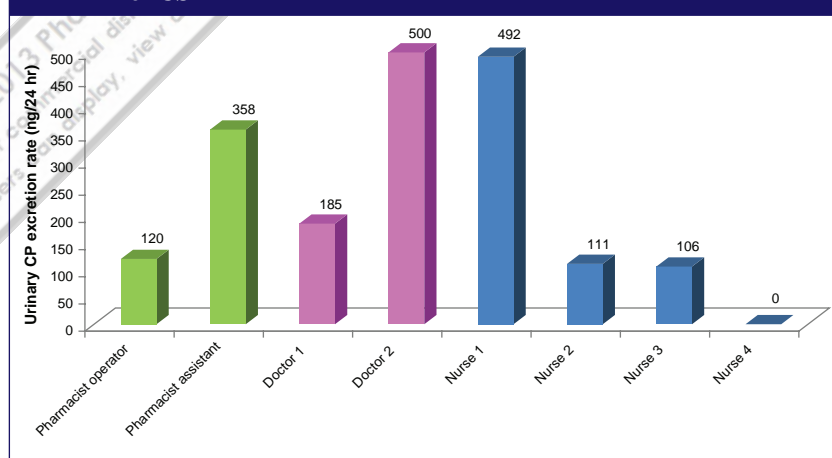
After six months of using the CSTD, levels of surface contamination with 5FU and CP were lower. However, still high levels of contamination were found mainly for 5FU in the nursing room and to less extent with CP in the pharmacy. At most positions contamination remained at the similar level. Surprisingly, levels of contamination with 5FU were higher on the floor in the nursing room. This result indicates spillage during administration of the drugs. After consultation with nurses, it was found, that not all nursing personnel complied with procedures, and devices were not being used correctly. Nurses disconnected elements of the closed system, leading to spillage during connection and disconnection of chemotherapy preparations from patients.

Table 1: Amounts of CP and 5FU in wipe samples [ng/cm²] before and after implementation of the CSTD

Surface description	CP [ng/cm ²]		5FU [ng/cm ²]	
	Before	After	Before	After
Pharmacy				
Surface of BSC	0.05	0.04	ND	ND
Airfoil of BSC	3.99	0.19	10.23	ND
Floor in front of BSC	8.33	2.96	ND	ND
Checking counter in the clean room	1.45	1.46	ND	0.80
Counter in the anti-room	0.56	0.06	ND	ND
Handle of airlock window	3.20	1.58	ND	ND
Chemotherapy ward				
Checking counter at nursing room	0.02	ND	1174	686
Waste bin lid	0.02	0.04	12.24	6.02
Floor by the armchair in nursing room I	0.64	6.19	19.54	43.57
500 mL IV bag after administration	ND	ND	ND	ND
Floor by the armchair in nursing room II	0.64	0.59	7.89	3.86
Armrest	0.09	0.15	ND	ND

BSC: biological safety cabinet; ND: no data.

Figure 1: CP in urine samples of hospital workers before implementation of CSTD



The results for CP exposure after implementation of the CSTD show that the workers were still exposed to CP but the level was strongly reduced. However, it should be noticed that the decrease of exposure to CP does not have to be directly connected with the use of the CSTD, especially since surface contamination was still observed.

One drawback of this study is that it involved a small number of participants, so more research is needed. Nevertheless, there is sufficient evidence that personnel who are not directly involved in handling antineoplastic drugs can be exposed to these agents. Thus, all healthcare personnel, not only pharmacists, working in or near areas where cytotoxic drugs are handled

must be made aware of the potential for contamination, and must improve safety procedures to reduce exposure.

This goal requires a continuous effort in investigation and research to introduce new approaches such as evaluation of different self-contained systems, assessment and validation of specific and general procedures, and their implementation in the daily routine of hospital departments. Adequate education and training of the staff members involved is essential.

Safe handling procedures should be implemented in all areas where antineoplastic drugs are delivered, stored, prepared, administered, and disposed of in order to reduce contamination in the workplace and the resulting exposure to healthcare workers.

The possibility of developing devices for the whole handling procedure must be addressed. It is important that other hospitals, particularly those in other countries, are involved in future research in this area in order to collect data on an issue that can no longer be ignored. The awareness of establishing processes and procedures has to be increased among other hospital workers, not only pharmacists, nurses, technicians and doctors.

Devices can be helpful in supporting safe handling of antineoplastic drugs, but they must be used correctly by adequately trained personnel, otherwise they become useless.

Acknowledgement

The authors would like to thank Dr Paul JM Sessink for analytical support and reviewing the manuscript.

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Clinical rule on safe methotrexate prescribing and dispensing in The Netherlands

A national clinical rule for proper handling of methotrexate was developed and implemented in The Netherlands in 2010 following a number of fatal incidents. The aim was to increase patient safety by preventing dispensing errors. Interventions implemented and results obtained in two hospitals are discussed.

Introduction

When prescribing medicines, physicians must be aware that medications can cause considerable harm as well as yield many benefits. Physicians must continuously consider many drug- and patient-specific characteristics during treatment. Appropriate use of information technology, especially the introduction of clinical decision support systems, can substantially reduce medication error rates and improve patient safety [1-3].



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and adverse effects. In the field of oncology pharmacy, prevention of medication errors is also especially relevant. Medication errors related to chemotherapy are among the most deleterious. Therefore, pharmacists as members of the oncological team should actively participate in quality management outside the pharmacy and conduct their efforts to reduce medication errors within the pharmacy by implementing clinical rules and records.

In The Netherlands, the occurrence of a number of fatal incidents in the administration of methotrexate prompted the development and implementation of a national rule in 2010 to ensure proper handling of methotrexate in pharmacies. The clinical rule aimed to increase the safety of patients by preventing dispensing errors. Most hospital and community pharmacies implemented this clinical rule. In this paper, we share our daily practice in the Divisions of Clinical Pharmacy, Onze Lieve Vrouwe Gasthuis, Amsterdam, and in the St Elisabeth Ziekenhuis, Tilburg, The Netherlands.

What is a clinical rule

Computerized physician order entry (CPOE) with clinical decision support has been promoted as an effective strategy to prevent the development of a drug injury, defined as an adverse drug event [4]. The clinical pharmacist will define rules to increase medication safety by combining patient-specific medication data with clinical chemistry parameters, and the subsequent application of medication rules. After entering medication orders into the database, a signal or alert arises from the clinical decision support system. Thus, a clinical rule is an algorithm in which patient characteristics are linked, with the aim of generating patient-specific reviews or advice to improve patient safety. The system gives the pharmacist a list of patients at risk, with applicable directives, rather than having to search for these patients by hand. By using clinical rules, the pharmacist can specifically focus on patients at risk and, therefore, save time.

We are particularly interested in clinical rules that contribute to medication safety and that prohibit the occurrence of toxicity

Why a clinical rule for methotrexate

Methotrexate is a drug with different indications and strongly different dosage regimens. In oncology, administration occurs often on a daily basis, depending on the chemotherapy scheme (up to several grams per day); however, in rheumatology and gastroenterology, the drug is given in weekly regimens (5–30 mg). Some fatal incidents occurred in The Netherlands when methotrexate was taken daily instead of weekly by rheumatology patients. In some clinical cases, methotrexate was given to the patient for several consecutive days before the mistake was realised. Methotrexate was stored on the ward, making this possible.

These incidents were recorded in the *Centrale Medicatiefouten Registratie* (CMR), a central medication incidents registration system. The system was developed in The Netherlands in 2006 as a nationwide incident reporting system and web-based application for reporting medication-related incidents [5]. Medication error reports from participating hospitals are collected and stored in the CMR database. This is especially helpful for serious medication errors. In these cases, special ‘alerts’ are sent to all participating hospitals, together with recommendations to prevent the same error happening again. One example was an alert for once-weekly methotrexate dosing. This regimen was switched inadvertently to once-daily dosing a number of times in The Netherlands, and in other countries, sometimes with fatal consequences. For this reason, CMR alerts were sent to all hospital pharmacies, and warning letters issued by the Dutch Healthcare Inspectorate. The CMR also issued a set of recommendations [6]. Analysis of the incidents

and recommendations about methotrexate prompted the Dutch Association of Hospital Pharmacists to draw up national guidelines for prescribing and dispensing methotrexate to ensure proper handling of this drug, visit www.knmp.nl. Pharmacists were asked to pay special attention to these patients and to take precautions.

Recommendations from the CMR

The CMR's main recommendations reflect the events that are most error prone in the distribution chain: 1) every prescription for methotrexate should be checked for indication—which would demonstrate whether a weekly dosage regimen is appropriate—and dosage; methotrexate should only be prescribed by physicians experienced in prescribing and monitoring methotrexate; 2) the pharmacy computer or the CPOE can be set to give an alert for each dose of methotrexate, whether it is correct or not, to facilitate the checking process stated above; 3) methotrexate should only be stored in the hospital pharmacy and not on the wards; 4) each methotrexate weekly prescription should be dispensed for a maximum of one week; this should be recorded per patient with the date of dispensing, in order to prevent another employee from dispensing the methotrexate again the next day; 5) in the hospital pharmacy store, a message should be displayed in the methotrexate area reminding everyone not to dispense for more than one week; and 6) physicians, nurses and pharmacy technicians should be trained about methotrexate [6].

Results

The recommendations and national guidelines were implemented in the Onze Lieve Vrouwe Gasthuis, Amsterdam, and in the St Elisabeth Ziekenhuis, Tilburg, The Netherlands, as a clinical rule for physicians, nurses, pharmacists and pharmacy technicians. Results of the implementation of a clinical rule for methotrexate used in patients after three months are listed below:

- No storage of methotrexate on wards
- Dosage control in the pharmacy for all prescriptions
- 100% alert in CPOE
- Dispensing only after authorization by a pharmacist
- Dispensing the medication needed for only one cycle
- Date of delivery recorded
- Medication review carried out for each patient on methotrexate for rheumatology, gastroenterology or oncology, with emphasis on drug–drug interactions and renal function
- Enquiries made to prescribing physicians about whether drugs should be taken or omitted during hospital admission
- Interview with patients about exact use of methotrexate, e.g. indication, dosage, day of administration, and use of folic acid
- Use of tablet strengths of 2.5 mg only
- Tablets, syringes, or IV infusions delivered by the pharmacy; use of patient's own medications not permitted to prevent errors

Pharmacists and pharmacy technicians were asked to follow a flow diagram and a standard operating procedure, entitled 'Methotrexate: prescription order entry, medication surveillance and logistics'. The purpose of this standard operating procedure was to describe the additional precautions taken in processing a methotrexate medication order for a clinical patient. The procedure described in this document is applicable to all methotrexate medication orders, injections and tablets, for patients admitted to the hospital. Communications to physicians and nurses about additional precautions in processing a methotrexate medication order for a clinical patient were made through various communication channels, e.g. hospital pharmacy websites, various newsletters, and CPOE classes. Key points are as follows: 1) all methotrexate products are at product level in the CPOE (Theriak and Navision Pharma), flagged as consultation medicine to ensure that medication orders for these products are always caught in the buffer zone. This means that every methotrexate medication order is reviewed by a pharmacy technician and a hospital pharmacist before being dispensed; 2) orders for methotrexate solution for injection or infusion, methotrexate tablet, or liquid preparation for clinical patients, are entered into the CPOE by the physician or nurse, or submitted as a medication order to the distribution department of the hospital pharmacy. In the latter case, the pharmacy technician of the distribution department enters the order in the CPOE; 3) on entering methotrexate into the CPOE, the medication order is transferred to the medication alert buffer of the pharmacy technician and the hospital pharmacist on duty; 4) every day, a distribution pharmacy technician has 'methotrexate duty' to coordinate orders and dispensing, and to communicate with the preparations department about methotrexate injections, infusions and methotrexate liquid preparation, and the logistics department about methotrexate tablets; 5) the preparations department dispenses methotrexate for injection (on indication of psoriasis, rheumatism or Crohn's disease) or infusion (oncological indications); methotrexate liquid preparation for paediatric oncology can only be dispensed on the basis of a medication order authorized by a hospital pharmacist; the logistics department dispenses methotrexate tablets; and 6) the labels of the methotrexate syringes for indication of psoriasis, rheumatism or Crohn's disease, and the labels of methotrexate IV solutions, are provided with a bar code for administration recording purposes.

In both hospitals, we see between three and five patients a week, and screening takes about 10 minutes by pharmacy technician and five minutes by the pharmacist. Patients understand why we do this and are cooperative with the pharmacovigilance and medication surveillance.

Conclusion

With our practice, we contribute to increased patient safety. The interventions can be implemented in a short period of time and do not demand much time from pharmacy technicians

and pharmacists in our hospitals. This type of practice could be an important innovation for the pharmaceutical patient care on the wards in Europe. It can, however, be carried out in general practice, so both inpatients and outpatients can benefit.

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Integral oncology patient information system (OncoBASS): 5-year assessment

Ana Rosa Rubio Salvador, BPharm; José Manuel Martínez Sesmero, BPharm, PhD; Izaskun Alonso Aldama, MD, et al

Computerized drug-ordering software can prevent medical errors and provide benefits to the patient. The OncoBASS project was developed as an integral oncology patient information system. Five-year results from inception of OncoBASS in a general hospital are presented.

Introduction

The management of people with cancer is complex and hazardous. Chemotherapy administration is one of the most risky activities of modern medicine, because many of the antineoplastic agents have a narrow therapeutic index, and the consequences of, and error with, these drugs can be devastating. Many chemotherapy drugs have safety limits that cannot be exceeded. Additionally, in cancer chemotherapy, the dosage, and even the route of administration, have to be taken into account, because they may vary as a function of the tumour type and stage of disease.

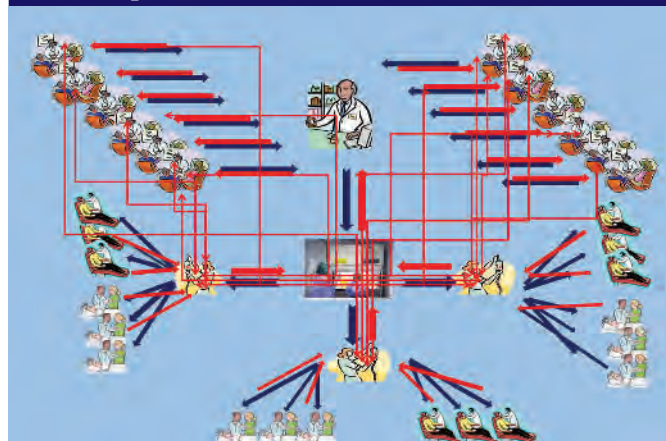
Clinical oncology involves many interconnected care processes provided by several medical specialties, including medical oncology, radiotherapy, surgical oncology, and pathology. Other healthcare professionals, i.e. oncology nurses, and pharmacists, are involved in diagnostic and therapeutic decisions, see Figure 1.

Strategies to reduce medication errors and improve the quality and efficiency of cancer pharmacotherapy care have been suggested by several organizations. These include the implementation of information technology, particularly computerized

physician order entry (CPOE) in hospitals and health systems as a consistent recommendation.

To achieve the best outcomes, it is essential to use information technologies to coordinate and integrate all the activities related to cancer care. Examples of electronic data generated

Figure 1: Complexity of cancer care involving different professionals



fering needs and who work in different functional scenarios, and manage large amounts of online data. Everything must be coordinated and work simultaneously, with enough fluency that the tool does not become an obstacle within the clinical process. In this way, reliable, safe and reproducible data can be maintained. For all these reasons, software that integrates the whole clinical process of a cancer patient, from diagnosis to death or recovery, remission, or death is difficult to find.

The main objective of the OncoBASS (OBss) project was to develop, implement and maintain an integral oncology patient information system (IOPIS) for use by cancer-care providers, and to amalgamate all the information pertaining to individual cancer patients, from diagnosis to the end of the treatment process. We present five-year results from inception of OBss in a general hospital.

Materials and methods

Clinicians, pharmacists, nurses, technicians and computer programmers worked in conjunction to develop and implement OBss as an IOPIS.

The functional philosophy of OBss as an IOPIS was based on three basic principles: (1) it should be user-friendly, requiring little, if any, training for clinicians; (2) it should allow clinical data to be updated while attending the patient on a clinical visit, but at no extra time cost to the patient or clinician; and (3) it should give as many (functional) rewards as possible, adding value to its implementation.

Four types of users were defined: (1) clinicians (oncologists, haematologists, paediatricians, and other clinicians responsible for cancer care patients); (2) pharmacists; (3) chemotherapy preparation personnel (technicians); and (4) nurses (responsible for chemotherapy administration). Each role is assigned a specific area within the system, with different functions and utilities. This prevents unauthorized actions by specific users. All the updated information is available to all users for consultation. A colour code was defined for each step in the process, to make it visible at a glance.

Clinician

The clinician is responsible for registering diagnosis, stage, surgery and biological markers. They are also responsible for updating clinical status, evaluating and registering response to treatment, and designing or incorporating pre-designed therapeutic strategies.

Some specific considerations about the role of clinicians, and clinical management within the entire process, are presented below.

Tumour type

Once data on personal medical history and symptoms have been added, clinicians must select the type of tumour, e.g.

solid tumour, leukaemia or lymphoma. This selection takes the clinician to different functionalities for each type of tumour. Clinical, pathological, and surgical information necessary for each tumour type is presented to the clinician. The software was designed to filter data to be shown on the screen depending on the tumour selected. The information is sufficiently dynamic to allow the clinician to work only within the parameters needed to manage one specific type of tumour.

Original data from other software systems can be linked to OBss and updated. The estimated median time needed for introducing all the clinical information for a new patient is about seven minutes.

Tumour response

During the clinical process, it is possible to register the assessment of tumour response according to 'response evaluation criteria in solid tumours'. It allows the evaluation response for each tumour, stage, or histology during the clinical visit, and can be seen in terms of 'overall survival' or 'disease-free survival'.

Toxicities

It is also possible to register toxicities according to National Cancer Institute Common Toxicity Criteria during the clinical evaluation of the patient.

Integrated software

The software was designed to connect with other electronic hospital patient records within the hospital information system, to allow the management of integrated information about admission and discharge of patients to be undertaken. Additionally, other clinical software, i.e. laboratory software, pharmacy software, has been integrated, providing essential continuously updated online information, see Figure 2.

Treatment plan

Finally, the clinician can select, prescribe, and make the necessary adjustments to chemotherapy treatment for each patient through the drug-ordering software developed. This takes into account the specific clinical conditions the patient has at the time the prescription is dispensed, e.g. renal, hepatic or blood disorders, and any other circumstances that might modify the treatment plan, e.g. drug allergies, drug-drug and drug-disease interactions.

Pharmacist

The pharmacist is responsible for ensuring that chemotherapy is used rationally and safely. They work within a multidisciplinary team, and are involved in the following: developing treatment strategies; definition and validation; design of the CPOE system; follow up of treatment plans; definition of alert system for drug allergies; drug-drug and drug-disease interactions; and drug dosing in special clinical conditions. Pharmacist responsibilities are discussed below.

Clinical data

Tumour data, staging system, clinical comments

X-ray and labs

Toxicity values

Protocols doses and administration data

Pharmacists are responsible for defining policies and procedures for conditioning the drug in a solution mix to be ready for use in the safety area by technicians. They must also establish and validate cytotoxic compounding procedures according to good manufacturing practices for reconstituting, diluting, mixing, packaging, labelling, and delivering antineoplastic agents in the most appropriate conditions to prevent errors.

Pharmacists are responsible for chemotherapy order validation. They must take into account established alerts for allergies, interactions and doses according to clinical condition, and defined alerts for stability of drugs in solution and storage conditions. Additionally, the pharmacist must ensure that the schedule is maintained as planned and contribute to managing the circumstances for failure to maintain it, see Figure 3.

At this point, pharmacists can adjust drug doses under some security limits previously defined by consensus (2.5%), and can select the most suitable brand-name drug for compounding that particular mix.

As part of the team, the pharmacist is responsible for the error-prevention programme and established monitoring plans for the whole process.

Once the pharmacist validates the chemotherapy cycle, technicians can begin to compound the cytotoxic drug according to procedures of good manufacturing practices established. A pro-

[illegible]

Technicians select the vial of drug and diluents proposed by the software according to some pre-established parameters of expiration, efficiency, and the way that every residual amount of cytotoxic drug is used.

The solution bag with the drug mix is weighted for quality control, the software sends an alert and does not permit continuation if there is any anomaly in the quality parameters previously established. All the data resulting from this process are registered for any later processing, see Figure 4.

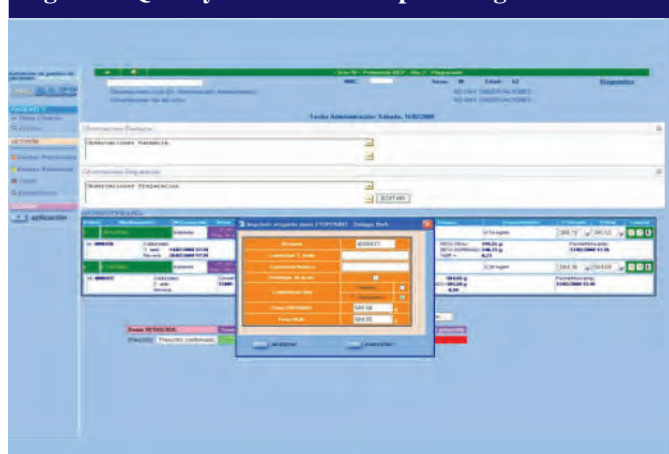
Compounded antineoplastic medications are labelled immediately after preparation. Labels are automatically printed. The following information is automatically generated and included on the label: patient's name, location, generic drug name, dose, route of administration, storage specifications, other specific information for a particular admixture.

The naming of the patient for whom the admixture has been prepared, and details of hospital location, can prevent errors being made when delivering the chemotherapy to the hospital facilities where the patient is waiting.

The ready-to-administer dosage is dispensed immediately after preparation, to assure minimum waiting time for the patient to be attended. They are dispensed according to the internal established procedures for maintaining appropriate storage conditions and preventing errors.

When a preparation is completed, a nurse is notified through the colour code established for every step in the process, and may begin to prepare the patient, i.e. beginning the infusion of IV premedication.

Figure 4: Quality control for compounding



The software allows the nurse to notify the pharmacist if the patient is ready to receive chemotherapy in cases of pre-prescribed cycles, i.e. cycles prescribed days before the date of administration, and preventing wasted preparations in advance should the patient miss the appointment.

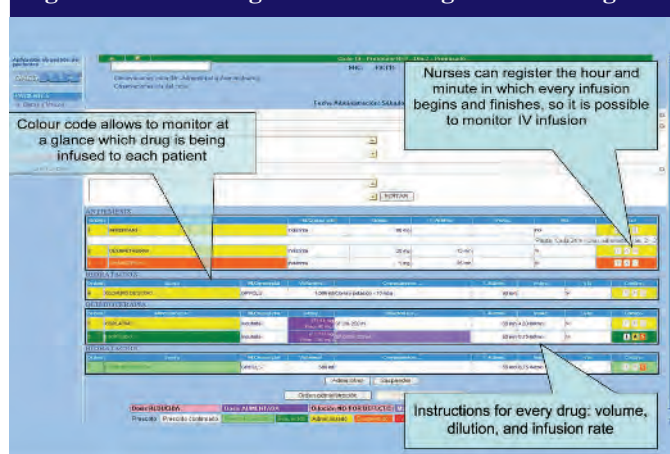
In the process of delivering chemotherapy, nurses can check the software for information on starting and finishing times, including every single drug that is prescribed in any step, e.g. hydration, and any other concomitant drug to chemotherapy, see Figure 5.

To follow up the implementation of the OBss project, the multidisciplinary team defined users, number of patients, department responsible for the prescription of a patient, and results from activity in the safety area, e.g. number of admixtures prepared to deliver antineoplastic drugs ready to use, as quality outcomes to be evaluated.

Results and discussion

The OBss software, designed as an IOPIS, was implemented in January 2007, and has been continuously updated over the past five years.

Figure 5: Monitoring screen including colour coding



A multidisciplinary team composed of physicians, pharmacists, nurses, technicians and computer programmers was created to follow up the implementation of the OBss project. This team has been working together during that time to review, modify, and implement new functionalities in response to different needs requested.

The usage rate among clinicians for OBss was 100% in January 2012, and integration with other health-information technologies, e.g. laboratory, radiology and pharmacy, available in the hospital has been completed.

Users

The OBss software is used by over 157 different healthcare providers: 23 oncologists, 13 haematologists, 18 pharmacists, 24 technicians, and 79 nurses, see Figure 6.

In the past five years, the number of users has progressively increased. The group of cancer-care providers that has grown the most is nurses, see Figure 7.

Chemotherapy treatments

OBss has been used for about 98% of all chemotherapy treatments, including those that do not have to be conditioned in a safety area, e.g. antineoplastics for oral administration.

One-hundred per cent of diagnostic and clinical data are registered on the system, including essential data required for prescribing specific drugs, e.g. human epidermal growth factor receptor 2 status. One-hundred per cent of biochemical data necessary to prescribe new chemotherapy cycle are also integrated online at the point of prescription.

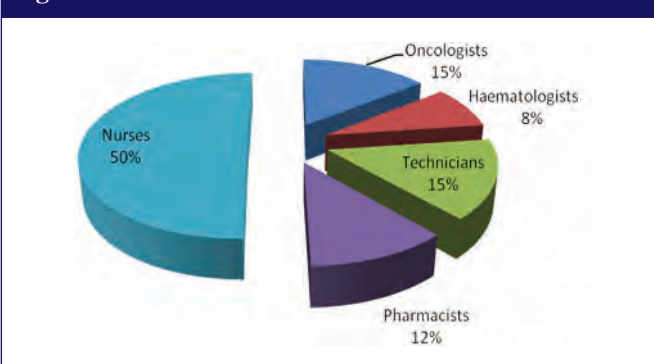
Admixtures

Admixtures are used in over 4,031 patients, with 46,612 preparations delivered: oncology patients (40,944 units; 88%); haematology patients (5,688 admixtures; 12%).

Patients

During the past five years, 4,031 patients have been treated, 3,960 (98%) were oncology patients and 71 (2%) were haematology patients.

Figure 6: OncoBASS users 2007–2012



Attendance figures for oncology and haematology patients between 2007 and 2012 are presented in Figures 8 and 9.

Figure 7: Annual breakdown of OncoBASS users 2007–2012

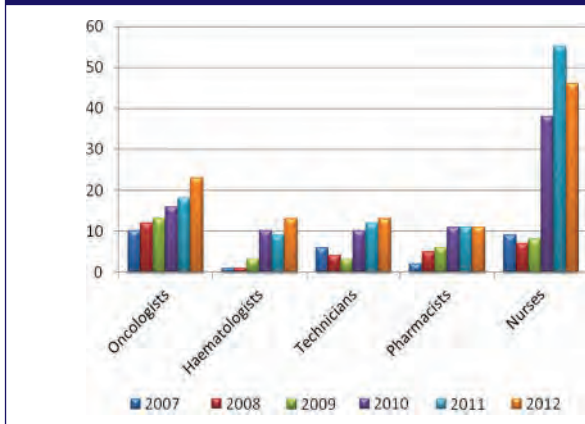


Figure 8: Oncology patients receiving treatment 2007–2012

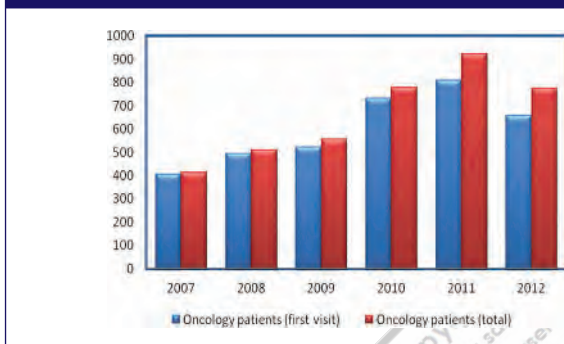
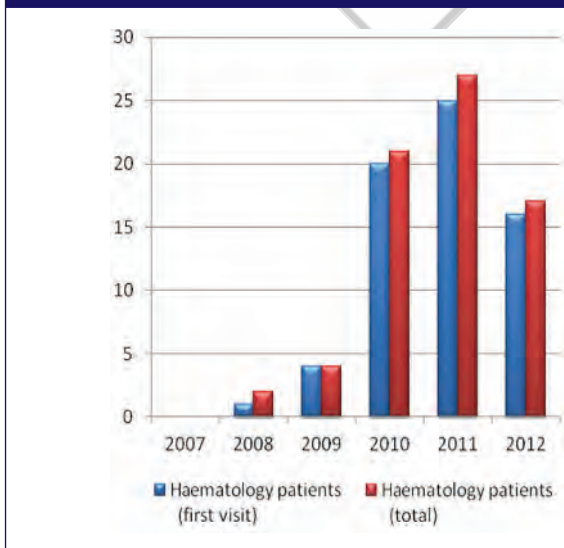


Figure 9: Haematology patients receiving treatment 2007–2012



Conclusion

The OBss project has achieved a 100% clinician usage rate, and has become a safe, fully-automated, integrated tool. Development is ongoing to support the delivery of best practices, improve quality of care and patient safety, and use data to improve accountability and enable better system planning and policymaking.

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Radio-frequency identification – a useful tool in the preparation and administration of cytostatics

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Improper handling or use of cytostatic drugs can endanger patients and hospital staff. The Masaryk Memorial Cancer Institute (MMCI) has implemented a system to improve the quality and safety of cytostatic drug preparation and administration based on radio-frequency identification tagging.

Introduction

The Masaryk Memorial Cancer Institute (MMCI) is a state-owned, medium-sized hospital with more than 200 beds and over 80 years of experience, that specializes in the treatment of cancer. The institute focuses mainly on the treatment of solid tumours, namely breast cancer and colorectal cancer. Patients are either hospitalized during treatment, or receive treatment at the outpatient clinic which is less expensive and also has psychological benefits for the patient. The ratio between outpatients and inpatients receiving chemotherapy is approximately 3:2.

Administering the incorrect dosage of cytostatic agents can endanger the patient. Handling them also presents a potential safety hazard for hospital staff. In order to improve the quality and safety of cytostatic preparation for the benefit of both patients and hospital staff, the Pharmacy Department at MMCI designed and implemented a system that recorded who, where, when and how an individual was exposed to cytostatics. Furthermore, pharmacy staff wanted to introduce active support software that would help them during the whole process, thus reducing the possibility of error. The outpatient clinic was also included in this project so that the administration of cytostatics could be recorded and supported there too.

Although there are several ways to monitor the preparation and administration of cytostatic drugs, radio-frequency identification (RFID) was chosen because it appeared to offer greater advantages than other systems, i.e. various bar code systems.

Disadvantages of the previous process

Prior to the introduction of RFID technology, there were several steps in the preparation and administration of cytostatics during which an error could potentially have occurred. However, because the pharmacy at MMCI has a quality control system in place, and is regularly inspected and audited following EN ISO 9001:2008, no significant errors have ever occurred. Other safety and quality control mechanisms included personnel watching each other during drug preparation, and strict adherence to standard operation procedures. The possibility of a patient receiving a drug intended for another patient was excluded. However, the person preparing the infusion could accidentally take the necessary volume twice and unknowingly

double the dose. It was not possible to identify such an error prior to the introduction of RFID. Furthermore, in some cases, it was also not possible to track the drug batch number during the process; this information is important with respect to unexpected adverse reactions.

As the patients or their relatives had to carry the prescription to the pharmacy in person, and sometimes did not want other people to know they were undergoing chemotherapy, they often folded the prescription and put it away. In some cases, they would forget to give the prescription to the pharmacy resulting in delayed treatment.

Since cytostatic drugs have limited stability, the date of first use was recorded on the vial. However, if the incorrect date was written on the vial, or the date became smudged and illegible, there was a risk that a drug of compromised quality may be administered to a patient. Furthermore, access of personnel to the drug preparation room was recorded in written form. Looking for particular entry in the records or counting annual sums for individuals was difficult. Further, erroneous entries were difficult to identify.

Technical solution

RFID technology is based on the communication between a unique carrier of information, i.e. a RFID tag, and a suitable reader. Widely used for identification and tracking purposes in industry, warehouses and supermarkets, this technology has recently found its use in health care [1-3]. A report prepared by RAND in 2009 [4] for the European Commission described seven cases of the use of RFID technology within the healthcare setting. In one case, the project funding failed completely. In two other cases, RFID was replaced by another technology for financial reasons. In both cases, RFID was used in hospital pharmacies—one of which was at the University Hospital in Geneva, Switzerland—to control the preparation and administration of drugs [5]. The RAND report praised RFID technology for its ability to increase the quality of health care, however, the report highlighted its high cost as compared with other technologies such as bar coding. RFID technology has also been used in a hospital pharmacy in Akita University Hospital, Japan. It is used in two other hospitals in the Czech Republic for the management of laundry and medical devices. Another hospital in the Czech Republic has announced its plan to

introduce RFID identification in the management of blood and blood products.

Whether to employ bar codes or RFID technology was discussed at the beginning of the project at MMCI. RFID was ultimately chosen because the use of radio frequency provides better reliability than systems based on visible light. Moreover, an RFID tag is not as prone to incidental damage as a bar code which can become smudged or may be printed illegibly. Additionally, RFID tags can be placed on vials already possessing a bar code without the risk of having two different bar-coding systems on one vial. Drug manufacturers put bar codes on their labels; however, these are batch-unique, not vial-unique and this was not the case at the start of our project. Increased precision in drug labelling also allows more information to be stored.

In the course of the project, tags of other standards such as I-CODE and other working frequencies were tested. However, staff at MMCI chose passive RFID tags, ISO standard 15693, frequency 13.56 MHz. These cannot be used at distances greater than 50 cm. The proposal that evidence of staff entry into the preparation room could be tracked by finger rings with RFID tags and recorded by a walk-through frame with RFID reader working with UHF (800–900 MHz) frequency was abandoned. The system in use at MMCI may require more input from staff; however, it is clear whether personnel are entering or leaving the room, or simply checking whether the reader is functional. Staff can clearly see if their entry was recorded correctly, or who is inside the drug preparation room without having to go and look.

The pharmacy at MMCI uses RFID tags in two different ways: adhesive labels for vials and infusion bags (on which the RFID printer prints further information), and identification cards for pharmacists, nurses, and patients.

Although there is evidence [6] to suggest that interference between the tag and the infusion bag is possible due to the conductive nature of the infusion medium in the bag, we have never experienced this. We have also never encountered any problems with interference between RFID tags and medical equipment such as infusion pumps. Such interferences are known with frequencies other than 13.56 MHz [7]. In Japan, the shortest distance permitted between a 13.56 MHz tag and medical equipment is 22 cm; however, testing has shown that the risk of interference is significant in high-output antennas only, and these are rarely used [8].

Cost is the main disadvantage of the RFID system. Although initial costs are comparable to bar code systems, running costs are higher. An RFID tag costs approximately Euros 0.25 which is more expensive than a bar code label (Euros 0.05). Because of inherent difference between these two systems, RFID tags will never be cheaper than bar code. Our determination to continue with the RFID system depends on the finances of

both the pharmacy and the hospital. However, if necessary, the bar code system could easily be reinstated. The change could be complete or partial, e.g. RFID tags could be used to label vials but infusion bags could be labelled with a bar code, thus saving money but retaining many of the advantages of RFID.

Three different information systems are involved in the preparation and administration of cytostatics at MMCI:

1. Hospital information system – GreyFox contains all patient information, i.e. reports, laboratory results and records, and a list of all current and previous chemotherapy protocols approved by the clinic's management team. Protocols that are no longer in use are listed for information only, and the physician is unable to download them from the system. The physician must use a particular protocol for specific diagnoses only. Only minor changes in protocol are permitted, i.e. the dose of the cytostatic drug can be reduced (the reason has to be recorded), other therapies such as antiemetics, antihistamines, ions, liquids and growth factors can be added or modified, and the days on which the drug is administered within the protocol may be moved slightly forward or backward.
2. Pharmacy information system – Medea is standard software used in Czech and Slovak pharmacies. It can be modified by adding new modules, e.g. to support drug preparation or staff entry monitoring. Both GreyFox and Medea are products of Stapro, a Czech software company that specializes in health care.
3. WebSphere – An information system that is used in the out-patient clinic (and in the future, possibly also in the inpatient clinic), is a simple application that was developed by IBM solely for the administration of cytostatic agents.

These three information systems exchange and store information and are also available as test versions, which are used for training purposes and for the development of new functionalities.

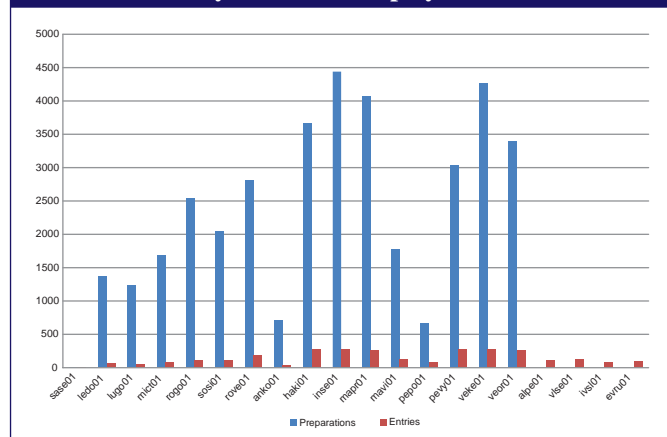
The whole system produces various data, as most operations are recorded to some extent. This enables retrospective control and also means the individual responsible for performing a particular step, and details regarding and how and when a procedure was undertaken, to be traced. These data can be further processed and analyzed and the results used to improve the process of preparation and administration of cytostatics.

Evidence of personnel

On entry to the drug preparation room, staff identify themselves with their personal RFID ID card. In this way, the identity of personnel who prepared cytostatic drugs is recorded. Recorded data are exported monthly and stored in defined folders where they may be accessed for internal and external audits. The number of entries as well as the total length of stay in the preparation room is recorded. The former

meets the requirements of law; the latter is more quantitative and may provide insight into the incidence of any occupational disease. Another important quantitative value is the number of drug preparations per person. This shows whether an individual was directly involved in the drug preparation process or had simply entered the room. Data for both number of entries and number of preparations for 2011 is shown in Figure 1.

Figure 1: Number of drug preparations and room entries made by individual employees in 2011



Active support

The isolators are equipped with RFID readers and touch screens, see photograph below, the computers themselves being outside the preparation room allow easier access. During drug preparation, the user reads the tag from the infusion bag and checks the data on the screen against the information printed on the label. Then, as individual vials are used, the user reads them thus deducting the volume that is needed to finish the preparation. The system remembers when a particular vial was first used thereby preventing the use of expired material.

The system allows for repeated preparation in case the infusion bag is damaged during or after preparation. If the infusion bag is not administered, it can be used for another

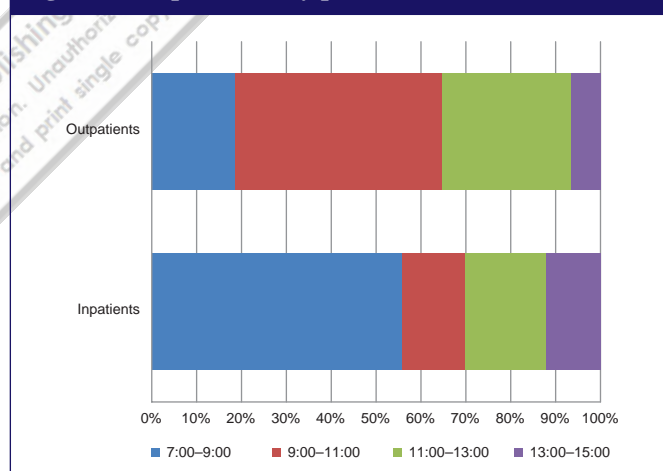


patient since the amount of drug in the bag is known. Any material necessary for the preparation is defined in the system and can easily be charged to a particular ward. In case of clinical trials, invoice for drugs and/or preparation is done automatically.

Data

Figure 2 shows the time of day at which drug preparation was most frequently performed in 2011. During the day, the amount of work is not divided evenly between particular shifts. Most drug preparations are processed in the morning. This is because prescriptions for inpatients, whose treatment protocols cover several days, arrive in the pharmacy first thing in the morning. Furthermore, outpatients usually arrive for treatment at around 9 a.m. Most outpatients like their infusions to be prepared in a very short timeframe, flooding both the pharmacy and the outpatient clinic with their requirements. An unwritten agreement between the pharmacy and the outpatient clinic states that patients should wait for their medication for an average of one hour (including the 15-minute recall period reserved for the physician).

Figure 2: Preparations by particular shifts in 2011



Conclusion

Since the project was implemented in October 2009, there have been no recorded incidences of erroneous preparation or administration of cytostatic drugs. Within the Czech Republic, MMCI is the only hospital that employs RFID technology in the preparation and administration of cytostatics, and is an example of a multidisciplinary solution tailored to the needs of the hospital. However, the general principle is robust enough to allow for implementation in other hospitals. The goal, i.e. the reduction of the human factor in the process of preparation and administration of cytostatics, was fulfilled.

From 2006 to 2009, the system was co-financed by Czech Ministry of Education, Youth and Sports (grant 2C06024). Currently, however, the costs are covered by MMCI, and form a standard part of the hospital budget.

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Storage containers for cytostatic agents: an overlooked aspect of shelf life

The need for extended shelf lives for cytostatic agents requires the use of appropriate storage containers. It is important that hospital pharmacies obtain further information from manufacturers of the containers in order to choose an appropriate storage container for compounded cytostatic agents.

Due to the increasing demand for compounded cytostatic agents, it has become necessary to increase the efficiency of the compounding process by using automated production. Getting the maximum benefit from automated production, ready-to-use cytostatic agents are produced in advance, and then stored for at least one to three months.

Containers for compounded cytostatic agents are made of plastic. Since automated production leads to an increase in storage time—in the range of several months—there is a substantially longer contact period between the storage container and ready-to-use cytotoxic agents, than with cytotoxic agents produced on-demand. As a result, it is important to establish reliable chemical and physical stability of the agent itself [1], and to also ensure that the storage container permits an extended shelf life.

Table 1 shows the containers employed for ready-to-use cytostatic drugs at two hospital pharmacies in Denmark.

As seen from Table 1, containers for cytostatic agents may include infusion bags (either empty or containing saline or glucose) pumps or syringes. Some of these containers are



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registered by the relevant authorities as a drug and some containers are CE marked. It is important to know if a container leaches any chemicals into the cytostatic agents; this may be determined in leachable and extractable testing.

Studies of leachables and extractables

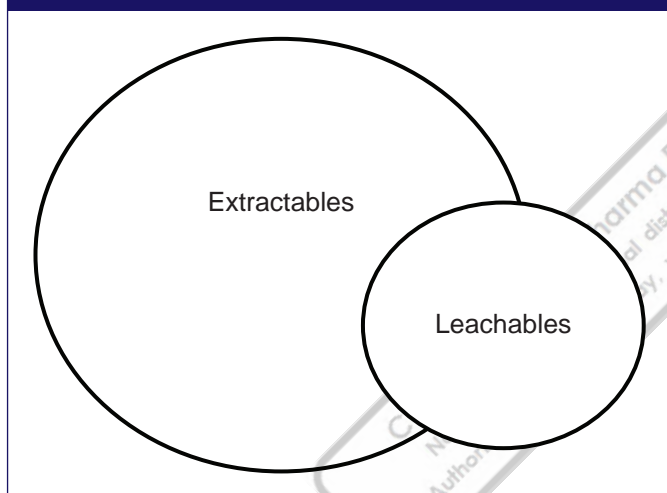
Leachables are chemical entities that migrate from plastic containers into a drug product, while extractables are compounds that are forced out of the individual parts of the container under specified solvent, temperature

and pressure conditions. Leachables are typically a subset of extractables, see Figure 1, and have potential to affect the product. Not all extractables are leachables and not all leachables correlate to extractables due to the fact that they are secondary leachables which is explained below.

Leachables and extractables are typically antioxidants, e.g. butylated hydroxytoluene, plasticizers e.g. phthalates, and unreacted monomers and oligomers from the polymerization of plastic. An example is bisphenol-A which is the monomer in polycarbonate plastic. Bisphenol-A is thought to have endocrine-disrupting effects and may harm newborns and infants up to 18 months of age. As a result, the Canadian Government

Table 1: Different containers used in the compounding unit at hospital pharmacy

Type of container	Manufacturer, product name	Approval of the container
Hospital Pharmacy A		
Infusion bags	Fresenius Kabi, Freeflex	Registered drug
	Baxter, EVA bags	CE marked
Syringes	Becton Dickinson, Plastipak	CE marked
Hospital Pharmacy B		
Infusion bags	Fresenius Kabi, Freeflex	Registered drug
	Baxter, EVA bags	CE marked
Syringes	Becton Dickinson, Plastipak	CE marked
	Terumo, Myjector	CE marked
Elastomeric pumps	Baxter, FOLFusor	CE marked

Figure 1: Relationship between leachables and extractables

has banned the use of plastic baby bottles that contain this chemical.

Plastic materials like polyvinylchloride, polyolefines and co-polymers are complex formulations that contain many impurities and additives representing thousands of possible leachables [2]. A number of analytical methods may be used to detect the presence and type of chemicals in plastics. For organic compounds, LC-UV-MS, GC-MS, GC-Head-space-MS, IEC, LC-NMR and TOC may be used, while ICP-MS, ICP-OES and IEC may be used to detect the presence of non-organic compounds. Due to advances in modern analytical methods, it is now possible to detect compounds in the parts per billion to parts per trillion range [2]. This in turn has led to the introduction of acceptance limits of leachables and extractables that may be contained within plastic containers used for orally inhaled and nasal drug products [3]. These limits have been recommended by a working group under the Product Quality Research Institute (PQRI).

While extractable studies are performed under exaggerated conditions, i.e. in the presence of organic solvents, accelerated temperature and pH, leachable studies are done in the presence of the drug product under normal conditions. Secondary leachables, which result from a reaction between leachable chemicals and the drug or excipients, cannot be identified in extractable studies. If the drug is a biological product, e.g. a monoclonal antibody, the interaction between leachables and the drug might lead to loss of activity or the development of neutralizing antibodies.

Infusion bags containing fluid

Infusion bags like Viaflo (Baxter) or Freeflex (Fresenius Kabi) that contain saline or glucose are registered as drugs and are approved by drug authorities to be stored for a designated length of time. The issue of determining whether leachables/extractables from this kind of container might leach into compounded cytostatic agents is assigned to hospital pharmacies. If the drug solution has aqueous properties, it is usually unnecessary to perform leachables/extractables studies. However, special caution should be taken with infusion bags made of PVC since entities such as DEHP may potentially leach into the contents of the bag.

When the container including the container closure system is part of a registered drug, and the compounding procedure at the hospital pharmacies is process-validated, the container would be microbiologically safe. However, hospital pharmacies must test the chemical/physical stability of a cytostatic drug within a particular infusion bag.

Although infusion bags appear to be the safest choice of container for ready-to-use cytostatic agents, they are not always ideal.

Manufacturers might alter the production process of a drug, or change the composition of a container without notifying hospital pharmacies—only health authorities are privy to such information.

CE marked containers

CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain European Directives. CE marking gives companies easier access into the European market to sell their products without adaptation or rechecking.

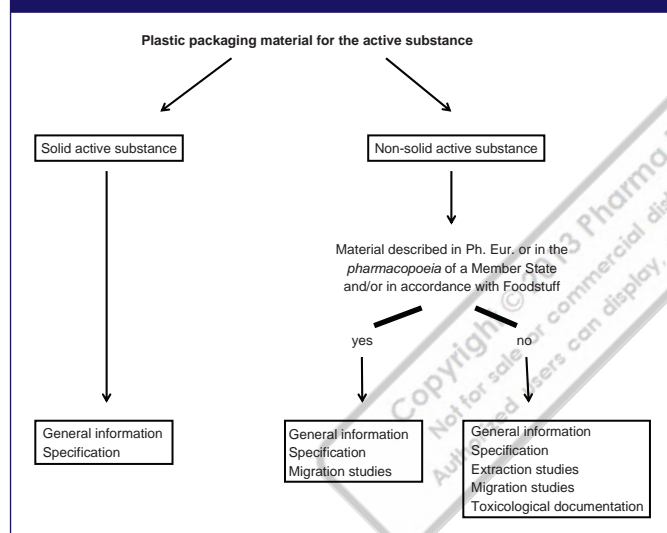
CE marked containers, also known as medical devices, include empty containers such as syringes, empty infusions bags like EVA bags from Baxter and pumps like FOLFusor. Although these containers are intended for immediate preparation and use of the drug, it is common practice for hospital pharmacies in Europe to use them for storing cytostatic agents. Syringes in particular are widely-used storage containers for cytostatic drugs. As such, it is surprising that the *European Pharmacopoeia* (Ph. Eur.) does not contain a monograph for plastic syringes used in this manner. Like infusion bags, changes in

the production and composition of CE marked containers may also occur without notice.

It is not necessary to perform extraction studies if the material of the medical device is approved by the Ph. Eur. or in the pharmacopoeia of a Member State. However, if the material is non-compendial, extractable studies should be performed on the container [4]. If the outcome of extractable studies suggests that a migration study—study of the release of leachables—is unnecessary, justification for the omission of this test should be provided [4].

‘Guideline on plastic immediate packing materials’ [4], published by EMA, provides a decision tree describing which documentation should be supplied based on whether the drug is solid or non-solid, see Figure 2. As shown in the decision tree, leachables from the container have to be tested, or justified whether or not the material is described in the Ph. Eur. or in the pharmacopoeia of a Member State.

Figure 2: EMA decision tree of required documentation based on whether the drug is solid or non-solid



Challenges for hospital pharmacies

There are points of similarities between the discussion of how to select the most suitable container and how to assign shelf life of cytostatic drugs. In both cases, hospital pharmacies bear the responsibility of choosing a safe container and assigning a safe shelf life. Further, as discussed earlier, changes in the production of either the cytostatic drug or the container may be made without the hospital pharmacies' knowledge.

Lack of traceability in the supply chain of medical devices also often makes it impossible to obtain information regarding the formulation of the polymer packaging. This problem goes further back in the supply chain since the suppliers of cytotoxic drug containers often are unaware of the production processes used by their suppliers. It is also difficult for manufacturers of the container to supply hospital pharmacies with

technical details because this information is confidential and not publically available, unlike if the information is required of a drug company for a drug registration where the container information is kept confidential.

Increasing shelf lives of cytostatic agents places extra responsibility on pharmacy staff who must ensure drug safety. This is because the drugs begin a 'new life' once they have been compounded [5, 6]. This requires hospital pharmacies to behave more like a drug company in that they must employ scientific/analytical procedures. Further, few hospital pharmacies have extensive material expertise or the analytical expertise to undertake material investigations as, e.g. extractables/leachables studies.

This highlights the need for a European centre of knowledge to house information from manufacturers and suppliers, in a way that allows hospital pharmacies access to important information whilst maintaining confidentiality. This solution would satisfy both the manufacturers' need for maintaining data confidentiality, and hospital pharmacies' need for recommendations regarding the use of cytostatic drug containers based upon scientific data.

Acknowledgement

The author thanks the Head of the Danish Research Unit for Hospital Pharmacy Dr Trine Kart for assistance during the preparation of this article.

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Cancer care in the Holy City of Karbala, Iraq

Following war and economic crisis, Iraq's health system is in a poor state. In the Holy City of Karbala cancer patients are among those who suffer the most. There is little privacy or opportunity for patients to consult with physicians, inadequate training of staff, and few medications available.

In the Holy City of Karbala we stood close to two beautiful shrines with golden roofs. We saw an old man near the tombs gracefully putting his face in mud. He said that the mud is from the tomb of Imam Hussein, grandson of the prophet Muhammad. His belief was that the holy mud would bring the gift of health from Allah and 'soak out' disease.

Many people with diseases as severe as this old man's believe in God. Their belief helps them to fight their disease burden, the suffering and worries, bringing patience and a way to withstand their disease. They strongly believe that a higher power will protect and support them. Cancer patients with terminal illness strongly emphasize their belief in spirituality. Their religion and reading the Koran give strong assistance and support.

In the governorate of Holy Karbala five hospitals with around 1,000 beds serve a population of about 900,000 inhabitants [1]. The largest is Al-Husain University Hospital, built in the year 1970 and managed by the Ministry of Health [2]. It contains different departments: surgical theatres, internal medical facilities, technical and administrative departments, among others. The hospital has about 700 employees divided into more than ten professional groups. Fifty pharmacists work in the hospital, illustrating the important role the pharmacists play. Like many other Iraqi hospitals, the funding received is hardly sufficient to cover salaries and recurrent expenses. Due to the huge number of visitors and expatriates who either visit or settle in the city, there is an urgent need to build at least 17 hospitals and healthcare centres in order to meet the needs of the health sector [2]. According to the annual report of Karbala province council for the year 2007, the most common causes of death among the population of the province are those associated with heart diseases, stroke, cancer and respiratory diseases [3], as in many Western countries, although the death rate from cardiovascular diseases seems much higher.

Cancer treatment and care

What follows is an account of our recent observations at Al-Husain University Hospital.

Cancer patients typically stay in mixed medicine wards together with, for example, surgical patients, patients with severe cardiac disease, and others. There can be up to around 50 patients per ward,



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divided into individual rooms or bays each accommodating between two and eight patients. Each ward is served by 15 nurses, as well as cleaners, a pharmacist and visiting physicians.

We have observed, however, that there is nowhere for patients to meet their family or friends privately. This can cause considerable chaos, the large halls fill up with visitors. The hospital

does not provide any active treatment for cancer, either radiotherapy or chemotherapy. Cytotoxic drugs are not available in any of the hospitals of Holy Karbala and patients have to go to Babylon for chemotherapy. Patients may get prescriptions for hormones which have to be bought at the patient's own expense and brought to the hospital for administration by a nurse.

Cancer diseases are of major concern, where most diagnoses are made at an advanced stage and the treatment and care are obviously seriously deficient. Many patients arrive too late for cure. Their care is focused on palliative support with pain relief, prophylaxis for nausea and vomiting, dyspnoea and other disease symptoms. Eventually patients leave the hospital and go home for a peaceful death. There is a pressing need for specialist oncologists, palliative care nurses, as well as well-trained clinical pharmacists in the Holy City of Karbala.

Drugs from the hospital dispensary are administered free of charge to patients [3]. However, the dispensary only stocks essential drugs and not all the drugs needed by patients. Patients that can afford to buy medicines from private pharmacies but the costs can amount to more than a monthly salary. Remarkably, we have found that some physicians help to pay for the drugs from their own pockets. On the ward, a clinical pharmacist dispenses drugs to patients but is seldom in obvious contact with them but may be consulted over pharmaceutical problems. The clinical pharmacist checks and signs for prescribed drugs, as well as the appliances used in the hospital, and distributes medicine to the various departments based on need. Outpatients or their relatives can collect prescriptions from the dispensary.

The procedure for having a consultation with a physician is complicated. On arrival at the hospital patients must wait in line to get a pass, which allows a visit to a dedicated physician. They then have to wait in line again to see the doctor. Even



From the ward



The old man

patients from outside Holy Karbala may have to wait for up to four to six hours for clinical investigation. The queuing is so disorganized that many patients show up really early in the morning to be sure of getting examined. Physicians might arrive late, further delaying the consultation. Some physicians fail to appear altogether, which creates large problems for those who have travelled a distance, including from other governorates. Drugs are prescribed based on patient's descrip-

tion of their symptoms rather than necessarily following tests. Follow-up appointments are sometimes put in a notebook but many patients are illiterate.

The hospital has a clear hierarchy in which the patient is the lowest. Consultations are often disturbed and the physician sometimes even leaves without any explanation. Without privacy, a patient is surrounded by other patients and 'listeners' while trying to give the physician his or her medical story and problems. Medical students may also be present. Even dying cancer patients can be present in the consultation room.

The hospital kitchen has a high standard of hygiene which may be due to an agreement with private restaurants to make food for the patients. There were guidelines as well but these are not followed.

In a recent study, a validated instrument to measure Quality of Life EORTC-QLQ-C30 in cancer patients gave a low score for overall functioning and a high score for symptomatology in those with advanced disease in the Holy City of Karbala [4]. The patients' scores for emotional, social, physical and role functions but not cognitive function were generally low, indicating poor overall quality of life. The frequency of treatable side effects from the disease and the treatment, such as pain, constipation, nausea and vomiting, indicated that there was only limited knowledge and resources available for patients. Fatigue, which seems to be one of the most reported symptoms among advanced cancer patients, showed a high association with other symptoms and functions. Qualitative studies have also revealed that the highest amount of social support

came from a patient's spouse, physicians and from his or her spirituality. Many of the advanced cancer patients focused on specific problems as a way to cope with their disease [4].

Our observations, together with these published studies, suggest an overall lack of sufficient relief of symptoms for cancer patients and lack of palliative care in Iraqi hospitals. Just one good relationship from a single source may provide an important level of support for patients. Spiritual coping and religious support, praying and reading the Koran, is of great importance as an additional coping element.

Perspectives

In the last decades, Iraq has been destroyed by war, sectarian conflicts, sanctions, and rigidly centralized and authoritarian rule. These conditions have increased the Iraqi grievance and economic crisis and led to a huge loss of human life [5].

Despite the country's rich natural resources, Iraq's human development indicators are now among the lowest in the region, and imply suffering from a double burden of diseases. There are major communicable diseases, along with cardiovascular diseases, diabetes and cancer which are all of major concern. Critical weaknesses characterize the management of the health sector in the country. A rational process of strategic planning, evidence-based decision making and a formal health policy is not available in Iraq. There exists no national insurance system or a system based on sickness funds [5, 6].

It is clear that Iraq currently faces enormous health challenges. Obviously, few other countries have experienced such deterioration in health status during the last two decades [5]. We have found the problems to be obvious for the cancer care in Holy Karbala. There is an urgent need to build and develop health centres and hospitals, and to train professionals to provide support. It is also important to educate palliative care physicians and nurses in order to respond to the patient's needs [3].

The provision of psycho-social care, nursing, symptom relief, rehabilitation and palliation in cancer patients should be based on the individual patient's needs including their own preferences and situation. Academically based, continuous and systematic screening may be the best way to help individual patients, taking into account their physical, mental, social and existential needs. A comprehensive picture of the patient's entire problems is needed in order to provide a comprehensive plan of action involving the appropriate specialists. Clinical pharmacists can play an important role in these procedures as well. This whole process is crucial for raising the quality of life for Iraqi patients [7].

In summary, Iraq has a dire need for studies to assess the needs of cancer patients so as to develop palliative cancer care units and the Iraqi health system in general [8].

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Update

Pharmacologic treatment of cancer-induced pain

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No essentially new drug to treat pain has appeared over the last decades. Pain treatment in cancer has although improved and more patients may demand and achieve substantial pain relief. A pain analysis is essential and treatment must be validated. Patients should be well informed about treatment goals.

Introduction

Pain is a subjective experience and the best way to evaluate the effects of treatment is to ask the patient. Pain is not an unambiguous concept, but several pain types with different mechanisms may occur simultaneously. Nociceptive pain due to activation of nociceptors in the periphery, the pain receptors, following injury to the tissue. The inflammatory pain type is sharp and triggered by even gentle movements. Another type of pain often radiating in nature is neurogenic or neuropathic pain. There is also a large portion of patients experiencing a pain of unknown origin that often varies in intensity and extent. Knowledge of pain components is important for the choice of treatment.

Pain signalling and nerve tracts

A number of biochemical processes occur in the injured area following tissue damage. There is release of bradykinin, potassium, histamine, serotonin, coagulation factors and others, as well as activation of prostaglandin synthesis which

stimulates various receptors including the different transient receptor potential vanilloid receptor to the nerve tracts that transmit the pain to the spinal cord where it connects to an upward path to the thalamus. From there further activation of different brain centres for learning, experience of pain, anxiety and localization of pain is propagated. An important relay centre in this process is the limbic system. There is also a descending system from the brain to the spinal cord that can inhibit the incoming signals from the periphery. Endorphins and enkephalins, e.g. endogenous morphine-like molecules, can also attenuate the incoming signals to the central nervous system (CNS).

Peripherally acting agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, may reduce the synthesis of prostaglandins and thereby desensitize nociceptors for pain stimuli. These drugs may also inhibit the prostaglandin enhancing effect in the CNS. Thus, the so called peripheral acting analgesics indeed may have a dual action on pain.

Pharmacologic treatment of pain

No fundamentally new drug principles have appeared for the clinical treatment of pain during the last 100 years. However, the introduction of the Pain Ladder by WHO has led to structured treatment and acknowledged that opioid drugs are important tools for cancer sufferers. The WHO ladder remains the mainstay of cancer pain treatment. However, it is based more on expert opinions than on evidence-based medicine and today the aetiology of pain is recognised as the most important indicator for treatment choice. A careful analysis of different pain components is important for choosing the most beneficial pharmacological treatment. The strong, sharp and burning pain sensitive to movements must be acknowledged in cancer and be adequately managed to decrease the patient's anxiety as well. NSAIDs are important in the treatment of inflammatory pain and combined with morphine, treatment of both peripheral and central components of pain can be successful.

Acetaminophen

Acetaminophen, paracetamol, is a mainstay in pain management for all pain as the drug has both analgesic and antipyretic properties, while the effect to decrease a swollen tissue, the peripheral anti-inflammatory effect, is very small, if any. The working mechanism of acetaminophen has only recently been elucidated with identification of inhibition of cyclooxygenase or block of the prostaglandin synthesis primarily in the CNS as being the most important. Acetaminophen has a short half-life of two hours. The agent probably has a ceiling effect and single doses of 15–20 mg/kg are not considered to provide better analgesic effect. A normal dose of acetaminophen produces mild analgesia and few side effects. Acetaminophen may cause serious liver damage with necrosis at doses greater than 10g to adults. In the body, a substance glutathione can reduce the toxic metabolites responsible for the damage, but in large doses, this protection is not sufficient.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have analgesic, antipyretic and an anti-inflammatory effect that reduce oedema and swelling in the injured area. The effect is exerted by inhibition of prostaglandin synthesis by peripheral blockade of the enzyme cyclooxygenase. As discussed above, a central prostaglandin inhibition might at least be part of this analgesic effect. Prostaglandins play an important role in regulating a variety of physiological functions, and a blockade of this system entails, in addition to the positive effects on pain, there are a number of side effects as well. NSAIDs are dispensed like many other painkillers according to their analgesic duration and half-life. This does not apply to aspirin which has an irreversible binding to the enzyme cyclooxygenase and the effects and side effects persist until the enzyme is re-synthesized. The most serious side effects may be seen in the gastrointestinal tract, but the adverse events are also seen due to longer bleeding time, less kidney blood flow and asthma symptoms. Aspirin should not be given to young children since they cannot metabolize metabolite salicylic acid and they may be exposed to a larger risk for metabolic acidosis.

On the market there are now selective cyclooxygenase inhibitors, COX-2 inhibitors, which may result in a reduced risk of some of the adverse effects of traditional NSAIDs. As a whole, NSAIDs, because of the high incidence of adverse events, should only be reserved for patients with a clear inflammatory component of pain. A short-acting agent such as ibuprofen may be the appropriate first choice.

Strong opioids

Strong opioids from the morphine group of drugs are primarily intended for post-operative pain or pain from malignancy. Strong opioids act via opioid receptors in the CNS and activate descending inhibitory pain pathways in the spinal cord, reducing sensory inflow from the periphery. They also decrease activity in the limbic system that reduces the unpleasantness of nociceptive stimuli. Opioid control is found in many organs, which can lead to undesirable effects. For instance, undesirable effects on the gastrointestinal tract with delayed intestinal passage may result in constipation which can be prevented with a liquid laxative. Opioid treatment may also cause sedation, nausea and sometimes vomiting. These side effects are transient because of rapid tolerance development. All opioids depress the hypothalamic–pituitary axis with possible reduction of many hormones leading to a variety of symptoms. Strong opioids may involve the risk of respiratory depression and addiction. The risk of dependence may though not hinder adequate pain management.

Morphine is the gold standard drug when a strong opioid is needed although no large differences in clinical effects distinguish the various opioids. Morphine has an excellent anxiolytic effect, which may be valuable in many situations. The agent acts both as parent compound and through the metabolites morphine-3-glucuronide and morphine-6-glucuronide. These accumulate in renal failure and can cause serious side effects. One of the metabolites, morphine-6-glucuronide, has a strong analgesic action of its own. In manifest renal failure, morphine is not used because of the risk of myoclonic seizures and CNS effects. Dose requirements can vary greatly between patients and is why an individual dosing with subsequent quality assurance of effects is important. Oral morphine treatment in acute and cancer pain reduces the patient's dependence on healthcare professionals, provides good opportunity for individualization, prolonged duration of action and less side effects. Long-acting morphine preparations may be an option in chronic pain with little fluctuation in intensity. The development of tolerance to the analgesic effect may sometimes occur.

Other opioids have been used in cases where morphine is contraindicated. Oxycodone has become popular recently because of its low concentration of active metabolites and the possibility to use it in renal failure patients. This is mostly clinical experience and no evidence is available from controlled clinical trials. Until recently, ketobemidone, an opioid agonist with similar efficacy and pharmacokinetic profile to morphine, was used for the same purpose. Opioids are also available in transdermal preparations (such as fentanyl) but with large difference in pharmacokinetics.

These have also found a prominent place in treatment of cancer-associated pain of longer duration. Further, in severe pain, opioids may be given by epidural or spinal administration to alleviate the worst symptoms of the suffering patient.

Combination of analgesics

Combination formulations of analgesics are usually avoided though the various components differ in mechanism of action, therefore, they are often not given in the full dose and the components often have different pharmacokinetic profiles. Upon repeated dosing, this means that a risk of overdosing of one component and under-dosing of the other may occur. The best compounded fixed drug combinations are those containing acetaminophen and the weak opioid codeine. Codeine is metabolized to provide about 10% by weight and has the same clinical effect and side effect profile as morphine.

New combinations of drugs targeting neuropathic pain are being tested, mostly based on gabapentin as primary compound.

Cannabinoids, alpha-2-adrenergics, nicotine, lidocaine and ketamine all represent drug classes recently tried for pain relief. The impact has so far been low and side effects may dramatically limit their use.

Clinical view on pain treatment in cancer

Pain is a subjective experience. Individual treatment is needed, as 'only the patient feels how much pain hurts, in what way it hurts and what helps'.

The pain signal calls attention to damage or malfunctioning in the tissue. Pain relief is essential to prevent the suffering patient from gradual deterioration and increasing stress signals to the brain. Continuous signalling is non-functional. Unfortunately, the physiology of pain and pain-relieving mechanisms gradually change with time in the afflicted patient. Nociceptors in the periphery are up-regulated and regulatory inhibitory pain tracts from the brain stem to the spine are attenuated so that pain signals are continuously amplified at the spinal level. Several targets for pain relief are physiologically down regulated during long-term pain. Therefore, common analgesics lose their effect over time even though doses are gradually increased. The exact mechanisms for this are not known, e.g. opioid insensitivity. Formation of an allosteric binding site changing the receptor properties or accumulation of metabolites with receptor antagonistic properties has been suggested. Also, opioid receptors taken from the cell surface into the cell resulting in less sensitivity is another possible mechanism. This has led to the concept of 'morphine rotation' in which one opioid is switched for another. Switching drug can result in better pain relief despite far lower than equi-analgesic doses being used. In a phase of resurgence, methadone is often used because of its unique receptor-binding properties. Co-administration of opioids acting on different receptors has become of interest. Thus, oxycodone supposed to have some kappa agonistic properties, may offer enhanced analgesia.

Neuropathic/neurogenic pain is common due to pressure of tumours on nerve tracts. This type of pain has always been difficult to treat and available drugs only give partial pain relief to a minority of patients. Current research points to promising results with the N-methyl-D-aspartate non-opioid receptor complex as a target. Amitriptyline has been the drug of choice but debilitating side effects hamper its use. New drugs such as gabapentin and pregabalin originally indicated for epilepsy have been introduced. Although frequently used, the clinical efficacy is limited.

In parallel, non-pharmacological methods, evidenced-based or not, are increasing in popularity. A wide range of methods other than drugs can be used for successful pain management. Specialists can add different types of nerve blockades, use spinal administration of drugs or choose other methods of controlled analgesic delivery. Complementary pain-relieving methods in clinical oncology such as low dose cytotoxic drugs or radiotherapy to minimise tumour pressure and radioactive strontium to destroy bone metastases or bisphosphonates to modify destructive bone catabolism may improve pain relief.

Conclusion

More effort has to be focussed on the concept of pain and pain behaviour taking into account sociological, psychological and emotional aspects as well as past pain experiences and coping strategies to achieve successful pain treatment in cancer.

Pain should be treated individually on the basis of a complete pain analysis:

- A well-informed and confident patient is a prerequisite for successful treatment
- Treatment of pain must be quality assured
- Acetaminophen and morphine are the basis of pharmacological pain treatment
- Anti-inflammatory agents are used only for inflammation in the pain diagnosis
- Combinations of analgesics should be avoided if individualized optimal treatment is needed. A fixed drug combination of codeine and acetaminophen can be accepted for ambulatory patients

Acknowledgement

The author would like to thank Dr Stephen Butler, Pain Clinic, Uppsala University Hospital, Uppsala, Sweden, for the valuable comments on the submitted manuscript.

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Hannah, you can do it!

Hannah, you can do it! is a guide of the difficult stages of leukaemia in children illustrated through the entire course of little Hannah's medical treatment. The issues are told in sensitive, humorous stories that offer the children entertainment and encourage their involvement.

Hannah, you can do it! is an illustrated guide through the difficult stages of leukaemia: from diagnosis to recovery. It clearly explains to young leukaemia patients the necessary examinations and treatments that will be part of their therapy, and gives parents practical and psychological assistance so that together they can better cope with the disease. The authors deliberately called the book an illustrated guide; it can be read by older children, read to younger children, and, for adults, it is a handbook and a workbook, because it includes interactive elements.

Sometimes, life changes from one moment to the next—as it does in the story told in this book. This is a true story. There is a real Hannah. After her diagnosis and treatment for leukaemia, today she is cured.

When leukaemia is diagnosed, overburdened parents demand a lot of information about the nature of the disease: the prognosis, the therapy, disease duration, medication and its side effects, care and hygiene measures. This illustrated guide sensitively takes the reader from the beginning of little Hannah's illness, through the entire course of her medical treatment. It fills gaps in knowledge and provides valuable psychological help, not only to children with cancer but also to their parents who, through reading this guide, can give information and emotional support to their sick child. The guide explains complex processes in simple words and vivid pictures to help children understand them and become cooperative partners in their own treatment. Difficult issues are conveyed through sensitive, humorous



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stories that also entertain children and encourage children's involvement. The aim of the illustrated guide is to carefully prepare children and adults for the disease and therapy and remove as much of the accompanying fear as possible. Those who can better imagine their enemy can work better together to defeat it.

A complex message simply told

Child-friendly medical explanations make up the bulk of the illustrated guide. The book explains that the human body is made of billions of small building blocks. It describes the functions of the body, for instance, circulation of blood, cell division, methods of examination, e.g. EEG, ECG, ultrasound, MRT, CT, X-ray, treatments and stem-cell transplantation. Expressions such as 'It does not hurt, just lie quietly', help the young patients understand and prepare themselves for upcoming tests. Another main topic is the cancer cell, which is graphically depicted in the book as a dark blue, soft cell cancer, which we have called Shaggy. This results in constructive conversations with children who have cancer and who try to visually imagine their own destructive cells. The cancer cell may not be evil, or too hard, sharp or too threatening in its entirety, because it is in the bodies of children. However, the cell must be seen as an unwanted intruder. Particular emphasis is also placed on the priority of taking medication, its effects, and its often unpleasant but unavoidable side effects. The guide's child-friendly explanations are intended to make it easier to give medication and trust in the medical and pharmaceutical industries.

The young patients are encouraged to imagine how the chemotherapy drugs damage and destroy their cancer cells. Such a visualisation process can promote recovery and strengthen the healing process to ensure that cancer is not seen as the finishing-line, but as a starting point into a manageable future.

Information is important

Many developmental psychology studies have shown that children's ability to understand and deal with medical information is usually underrated. Children are very capable of not only handling their physical condition, but also gruelling



operations if they are kept well informed. Therefore, it seems irresponsible to deny children information. It is during the exceptional situations when parents are trying to hide the truth, that children can feel most betrayed and helpless. These children face the risk of suffering trauma, and the additional danger that they lose all trust in medical staff and especially in their parents. Therefore, even small children, depending on their individual level of development, should be prepared for the therapy. To this end, we have incorporated into the story, tips for parents that are marked with symbols and coloured boxes. These give mainly psychological advice, but also tried and tested medical advice and practical tips.



Polly cuddle-cushion helps

Polly is Hannah's cuddle-cushion. It comes to life in the story and helps Hannah to be healthy again. One Polly comes with every book to ensure that each child has their own Polly for comfort and support. The cushion has a removable washable cover to meet hygiene standards. Polly represents trust, comfort, friendship, affection and security, as well as joy and fun.

Children have a different concept of time

Children generally have no clear notion of time; their concept of time is different to that of adults. This means that they require the idea of forthcoming procedures to be broken-up into small stages and explained in sequential order. They need an understandable reference point. The book includes a therapy-plan leaflet developed by St Anna Children's Hospital, Austria. The therapy plan consists of a Leporello, or seascape, with adhesive labels in the form of sea animals and a ship. The ship represents the position of the child. For every completed therapy, the child can choose a sea animal to add to the seascape, and advance the ship on its way towards the sun and into the harbour, where the child will be healthy. The medical therapy plan will be agreed with the medical personnel and the parents. Each child should have the chance to help design their own therapy plan. Additions can be made with coloured pencils and adhesive sea animals. In this way, the child is also engaged on an emotional level.

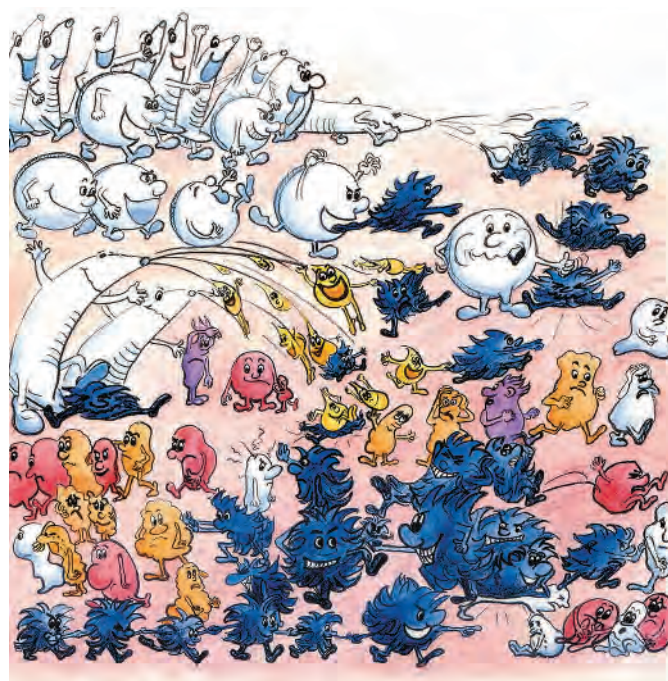
The friendly face of injections

Small children, pre-school children, concentrate on only the obvious aspects of their situation. In hospital, lots of machines, strangely dressed people in white coats or medical equipment can, therefore, make them anxious. The book includes stickers: eyes, noses and mouths to cut out and stick on. The sheets include different facial expressions or moods, which the children can choose to stick on the syringe or infusion bags as they wish. In this way, they tackle their fear of otherwise scary objects.



Pre-school children have an egocentric perception. They see themselves at the centre of the world and are convinced that everyone knows how they feel. There is, therefore, a place for children to draw for self-expression: their favourite place at home, and how their bodies feel.

Hannah, you can do it! is a complex book that won first prize in the City of Vienna's Health Awards in 2007. Since then, the book has been published in Arabic, English and Russian with further translations planned.



***Camillo Pastillo* – a children's handbook for understanding chemotherapy**

Said is not heard, heard is not understood, understood is not accepted! Doctors may think they have said everything, but this does not mean that the patient has understood the full message. The book titled *Camillo Pastillo*, aims to fill the gaps left when what is said is not heard, understood or accepted. It deals specifically with the effects and side effects of chemotherapy. A round pill in red rubber-boots called *Camillo Pastillo* does not want to be spat out by the children again and comes to life because it has so much to explain to the children. *Camillo Pastillo* talks about children's cancer and the authors introduce a range of chemotherapeutic agents in a language that children can understand, and explain how they affect the body, why they are administered and what side effects to expect.



The result is a better understanding of the effects and the side effects of cancer medicines. Hopefully it will make the many tablets easier to take and the illness easier to overcome.



Distributed through the Children's Cancer Help Parents' Initiative and free for children affected.

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