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EJOP • Volume 5 • 2011 • Issues 3-4 • €35

EJOP
European Journal of Oncology Pharmacy
www.ejop.eu

EJOP is published quarterly and mailed to more than 5,000 European oncology pharmacists, pharmacy technicians and subscribers in 33 countries; and distributed at major international and national conferences. EJOP is available online (www.ejop.eu).



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**ISSN EJOP:** 1783-3914
**Print Run:** 5,000 Printed by PPS s.a.

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



**Subscription Rates 2012:**

| | Europe | Non-Europe |
|---|---|---|
| Individual: | €135 | €159 |
| Hospital/University: | €297 | €321 |
| Corporate: | €378 | €402 |
| Student: | € 81 | €105 |

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



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EJOP is published quarterly. Subscription orders must be prepaid. Subscriptions paid are non-refundable. Contact marketing@ppme.eu for further information.

**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.

# Hope is a good breakfast but a bad supper*

Klaus Meier
Editor-in-Chief

EJOP

The discussion about the future role of pharmacy is ongoing and at the European level several proposals from ministries or the pharmaceutical inspection have been tendered along the way to describe the possible needs. We know that several lobbying groups are working in Strasbourg, France, as well as in Brussels, Belgium, to bring about different points of view about the position of pharmacists.

Unnoticed by the public, the path is being smoothed to ignore the resolution adopted by the Council of Europe Committee of Ministers in 1997 [1]:

- Recalling that the pharmacist's evolving role is to ensure the safe and effective use of medicines by patients at the lowest cost, thus contributing to the welfare of the patients and the improvement of public health;

- Considering the present trend to shift the focus of attention away from the preparation of medicines towards ensuring that they are appropriately prescribed and dispensed by pharmacists and correctly used by patients;

- Considering that this trend requires legislative reform and changes in initial training, and makes ethical demands on the profession;

- Considering that, in a changing economic and social environment, pharmacists must adapt and must bring up to date their knowledge, training and practice in order to play their full part in society;

- Considering that the patient's well-being must be at the centre of all pharmaceutical activity, that the pharmacist's traditional focus on the medicine must be shifted to the patient, and that the pharmacist should become a provider of health care in which the patient occupies the central place …

The understanding of the role of pharmacists is and was clear. Near to patients in collaboration with doctors, defining the multiprofessional work and improving their knowledge and expertise.

Since that time the ESOP has developed four new editions of Quality Standard for the Oncology Pharmacy Service (QuapoS), whilst keeping in close contact with the European Commissioner for Health and Consumer Policy. The goal is to unify national conditions for preparing cytotoxics and to educate healthcare workers as well as patients. This was no preterm birth that could not be followed by pharmacists Europe-wide. It is an open guideline with an option for each country to enshrine it in national legislation.

ESOP's understanding has grown that we have to foster collaboration with the European CanCer Organisation (ECCO) because a joint platform insures a multi-professional approach and the opportunity to be recognised as full partners of healthcare teams. A pharmacist will again be present on the board of directors in the next legislative period.

EJOP has now been published for five years and it plays its part in harmonising and encouraging the process of oncology pharmacy in Europe at the same time.

Again, in this issue we are presenting the efforts of national work in the report about the preparation of monoclonal antibodies as well as the general role of pharmacists in oncology trial management.

We get surprising views about the conditions for pharmacists from some countries. We can learn how in the UK the chemotherapy clinics can be led by pharmacists and follow the discussion from Saudi Arabia about hospital workers' understanding of nanotechnology. Often work at the national level triggers a European discussion. So, a questionnaire will be sent to all our 2,600 members about their understanding of nanotechnology in order to sensitise them to both the benefits and the risks.

As history has taught us that the revolution devours its children, we are aware we must show our responsibility every day in our daily work in each country. We are proud to celebrate in January 2012 the 20th NZW—clinical conference for oncology pharmacy departments—with nearly 1,000 participants and are sure that the first European Conference of Oncology Pharmacy in Budapest, Hungary in September 2012 will give all European oncology pharmacists a place of exchange and mutual support.

We are able and willing to work the whole day in not only the hope but also in the solid conviction that pharmacists, as we understand ourselves, are needed and welcome.

I am pleased and proud to be a president of such committed and convinced membership.

*Sir Francis Bacon

## Reference

1. Council of Europe Committee of Ministers [homepage on the Internet]. Resolution AP (97) 2 on the development of the function of pharmacists and the adaptation of their initial training. [cited 2011 Dec 15]. Available from: wcd.coe.int/ViewDoc.jsp?id=596013&Site=CM

# Preparation of monoclonal antibodies: practice across Europe

To ensure proper handling of monoclonal antibodies (mAbs), the hospital pharmacist has to consider the safety of the product, the safety of the patient, and the safety of the personnel compounding the drugs. We conducted a survey across Europe to investigate current practice.

## Introduction

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Ever since the first monoclonal antibodies (mAbs) became available, hospital pharmacists have been faced with the challenge of preparing them so that patients receive the correct dose, infusions are sterile, and pharmacy staff are protected from potentially harmful exposure. Formal studies investigating the risk of mAb-related occupational exposure have not yet been performed. Hence, when compounding parenteral formulations of these drugs in the hospital setting, the responsible pharmacist must subjectively assess the magnitude of risk. This raises several issues. Firstly, given that a large proportion of mAbs are administered to immunologically challenged patients, and sometimes with concomitant chemotherapy, a thorough aseptic technique which minimises the risk of microbiological contamination is pivotal.

Secondly, most mAbs are dosed using body weight or body surface area. Therefore, a safe and validated method of calculating the correct amount of infusion concentrate to add to the diluent is required.

Thirdly, occupational exposure of pharmacy and nursing personnel should be considered. Although most mAbs do not have a direct effect on DNA and are therefore not mutagenic or genotoxic, therapeutic exposure to some mAbs, e.g. muromonab, has been linked to tumour development [1], possibly via indirect pathways. Given that most hospital staff are only exposed to trace amounts of mAbs, this risk is likely to be very small. However, because evidence exists to show that rituximab, trastuzumab, and antiangiogenic mAbs such as bevacizumab, cetuximab and panitumumab can harm foetal development [2-5], handling guidelines are needed for pregnant or lactating hospital staff. Furthermore, because all mAbs are proteins they may cause sensitivity reactions. As yet, there is no way of establishing safe concentrations or MAC values of monoclonal antibodies for healthcare workers. Fortunately, when compared with classical chemotherapeutics, more stringent endogenous barriers exist against mAbs. Monoclonal antibodies have a relatively large molecular weight (about 150 kDa) and in the absence of special techniques such as microneedles or electroporation, are unable to pass the skin barrier [6]. Additionally, Monoclonal antibodies are extremely susceptible to denaturation induced by pH changes or gastrointestinal enzymes. Hence, oral absorption of these molecules is highly unlikely, but the risk of pulmonary absorption of mAB-containing aerosols, e.g. those created during vial reconstitution using syringes and needles, cannot be fully excluded [7].

Finally, one needs to consider whether it is safe to use the same equipment to prepare mAbs and cytostatics. In theory, it is possible that a safety cabinet or isolator could become contaminated with traces of chemotherapeutics [8-10] and if, for example, an infliximab infusion is prepared following a cytostatic compounding session, it may become cross-contaminated. Because drugs such as infliximab are generally administered on non-oncological wards, this contamination may then spread to other hospital departments where personal protection measures are not as strict as those of the oncology ward.

## Risk assessment

In The Netherlands, a mAb risk classification is currently being executed. Each drug is assessed using a standardised method that has been developed by an independent Dutch research institute (TNO, Dutch Institute for Applied Sciences), which includes an assessment of the drug's carcinogenicity, teratogenicity, and other toxic properties. Each drug is classified in one of five groups, with the highest class 5 being the most hazardous and class 1 being considered harmless. Cytostatics often fall into class 5. To assess toxic effects, exposure limits, material safety data sheets, and preclinical and clinical studies are reviewed. Using this method, mAbs generally fall into class 3 or 4.

Under Dutch national recommendations, compounding in a safety cabinet or isolator is recommended for class 4 compounds, whereas compounds regarded as class 3 require only the provision of personal protection (protective clothing and gloves). Thus far, five of the eighteen investigated mAbs have been deemed class 4 (alemtuzumab, bevacizumab, cetuximab, muromonab, panitumomab) and one (ibritumomab) has even been deemed class 5, based on its radioactivity. Further mAb classifications are listed in Table 1.

In Germany, a risk assessment of the most frequently used mAbs has been published [11]. After a thorough investigation

**Table 1: Risk assessment of monoclonal antibodies performed in The Netherlands**

| Name | Indication | Chimeric-human | Possible risk | Conclusion - class |
|---|---|---|---|---|
| Abciximab | Trombocytaggregation inhibition | Chimeric | No | 3 |
| Adalimumab | Rheumatoid arthritis, Crohn's disease | Human | Not likely | 3 |
| Alemtuzumab | Leukaemia | Human | Reprotoxicity, serious immuno suppression | 4 |
| Basiliximab | Organ transplants | Chimeric | Not likely | 3 |
| Bevacizumab | Colorectal/mamma carcinoma | Human | Embryotoxic | 4 |
| Cetuximab | Colorectal carcinoma | Chimeric | Embryotoxic | 4 |
| Ibritumomab | Non-Hodgkin's lymphoma | Human | Radioactive | 5 |
| Infliximab | Rheumatoid arthritis, Crohn's disease | Chimeric | Not likely | 3 |
| Muromonab | Organ transplants | Human | Carcinogenic | 4 |
| Natalizumab | Multiple sclerosis | Human | Not likely | 3 |
| Omalizumab | Asthma | Human | No | 3 |
| Palivizumab | Respiratory syncytial virus | Human | No | 3 |
| Panitumumab | Colorectal carcinoma | Human | Embryotoxic, decreased fertility | 4 |
| Rituximab | Non-Hodgkin's lymphoma, rheumatoid arthritits | Chimeric | Not likely | 3 |
| Trastuzumab | Mamma carcinoma | Human | Not likely | 3 |

of all available safety data, the study concluded that mAbs should be handled as hazardous substances and prepared in safety cabinets using maximum personal protection—as described in German national regulations.

## Survey of practices across Europe

To help us define a national guideline, we conducted an email survey amongst ESOP delegates. Thirty countries were approached, and completed questionnaires were received from 20 country representatives: Belgium (2 respondents), Bosnia, Croatia, Cyprus, Czech Republic, Denmark, Estonia (2 respondents), Finland, France, Germany, Hungary, Italy, Malta, Poland, Portugal, Slovenia, Spain, Switzerland, The Netherlands, Turkey. Two countries, Belgium and Estonia, provided two separate replies, resulting in a total of 22 completed questionnaires.

The first question asked was 'where and by whom in the hospital were mAbs prepared?' In 17 cases (77%), they were prepared in the pharmacy, in four cases (18%) they were prepared on the wards by nurses, and in 0 cases (0%) they were prepared on the wards by pharmacy staff. In some instances, however, mAbs for chemotherapy patients were prepared in the pharmacy, but mAbs for all other patient types were prepared on the wards, see Figure 1.

The second question asked was 'what type of equipment was used in the preparation of mAbs?' The vast majority of respondents (n = 15, 66%) used a safety cabinet. Five respondents (22%) reported using an isolator, and three respondents (14%) said no equipment or a crossflow cabinet was used, see Figure 2.

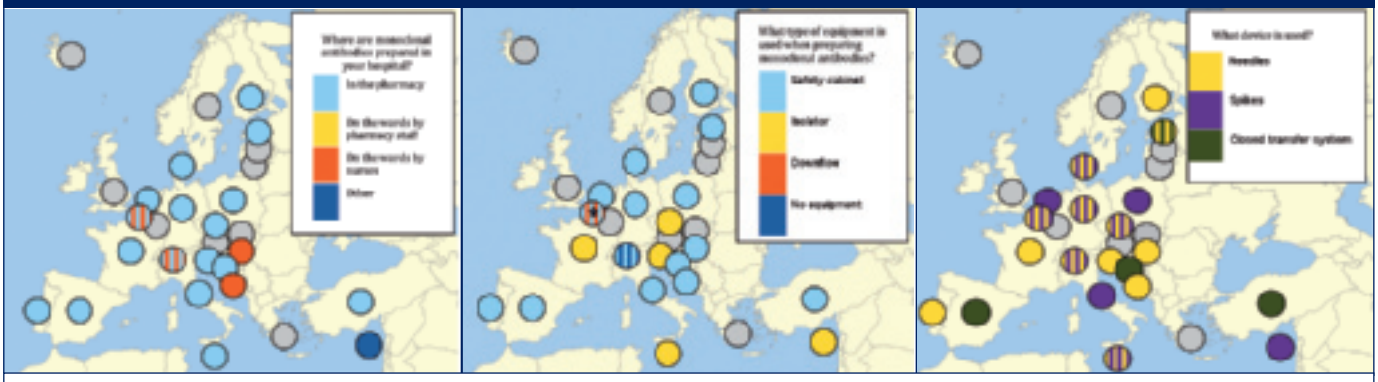
The next set of questions concerned the use of separate equipment for mAb preparation in non-chemotherapy patients. We asked these questions to review the possibility of cross-contamination, e.g. traces of chemotherapy residues on infusions for patients with rheumatoid arthritis or Crohn's disease. Because many ESOP members work in dedicated chemotherapy clinics, only nine respondents were able to answer these questions. Five respondents used a separate safety cabinet or isolator, and four respondents reported that mAbs and cytotoxics were prepared using the same equipment in non-chemotherapy patients. Respondents were also asked whether their compounding equipment was cleaned between mAb and chemotherapeutic use. Six respondents reported that such a procedure existed in their hospital, but 12 respondents reported that this was not the case. The other four respondents said this question was not applicable in their situation, mainly because they had separate equipment for these distinct procedures.

The final question asked was 'what type of transfer device was used when preparing mAbs?', see Figure 3. Responses to this question were diverse. Five respondents used only needles, four respondents used only spikes, and three respondents used closed transfer systems. However, most respondents (n = 7) reported that they used a combination of these devices.

**Figure 1: Where mAbs are prepared in your hospital**

**Figure 2: Type of equipment used when preparing mAbs**

**Figure 3: Type of transfer device used when preparing mAbs**



mAbs: monoclonal antibodies; Grey dots represent countries that were approached through the ESOP forum but did not return a completed questionnaire.

The results of our survey provided a clear impression of the variety of practice across Europe. In this respect, it was striking that in countries where two different hospitals completed the questionnaire, the responses also differed. This suggests that, in keeping with practice in The Netherlands, none of the surveyed countries have a broad consensus or guideline on this topic.

## Recommendations and QuapoS guidelines

In 2008, an ESOP technical workshop was held in Hamburg, Germany, and the subject of preparing mAbs, chemotherapy, active vaccines, and gene medicine was discussed. This workshop provided some recommendations on the issue:

- Cytotoxics and mAbs for cancer patients can be prepared using the same equipment.
- Monoclonal antibodies for non-cancer patients that have cytotoxic, mutagenic or reprotoxic (teratogenic) activities (CMR), should be prepared using safety equipment (safety cabinet or isolator) but in a different one than that which is used for the preparation of chemotherapy. If this is not possible, an appropriate cleaning procedure before and after the preparation must be established.

These recommendations are due to be incorporated in the next edition of the Quality Standard for the Oncology Pharmacy Service with Commentary (QuapoS). As a result of the Dutch risk assessment, we believe that this draft ESOP guidance is valid, but only for approximately one-third of mAbs, i.e. the ones that we believe have CMR activities, or that are suspected of being cytotoxic or teratogenic. In these cases, one should prepare the drugs in a safety cabinet or isolator, using spikes or closed devices, in line with the compounding practice for cytotoxics.

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## References

1. Orthoclone OKT3, Summary of product characteristics. Janssen-Cilag, 2010.
2. NIOSH. List of new FDA drugs and warnings fitting NIOSH criteria for hazardous drugs 2006. Available from: www.cdc.gov/niosh/docket/archive/docket105.html
3. Halsen G, Kramer I. Gefahrdungsbeurteilung monoklonaler antikorper der ATC klasse L01XC. Krankenhauspharmazie. 2009;30:441-53.
4. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes following maternal exposure to rituximab. Blood. 2011;117 (5):1499-506.
5. Shrim A, Garcia-Bournissen F, Maxwell C, Farine D, Koren G. Trastuzumab treatment for breast cancer during pregnancy. Can Fam Physician. 2008;54(1):31-2.
6. Mitragotri, S. Immunization without needles. Nat Rev Immunol. 2005;5(12):905-16.
7. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008;84(5):548-58.
8. Sessink PJ, Anzion RB, Van den Broek PH, Bos RP. Detection of contamination with antineoplastic agents in a hospital pharmacy department. Pharm Weekbl Sci.1992;14(1):16-22.
9. Schulz H, Bigelow S, Dobish R, Chambers CR. Antineoplastic agent workplace contamination study: the Alberta Cancer Board Pharmacy perspective. J Oncol Pharm Pract. 2005;11(3):101-9.
10. Mason HJ, Blair S, Sams C, et al. Exposure to antineoplastic drugs in two UK hospital pharmacy units. Ann Occup Hyg. 2005;49(7):603-10.
11. Halsen G, Kramer I. Forschung BGW. Bewertung monoklonaler anti-korper zum schutz beschaftiger. 30 Oktober 2008. Available from: www.bgw-online.de bestellnummer EP- BmAk

# The role of a pharmacist according to patients

From a patient's point of view, pharmacists play a key role in the healthcare team through the provision of high-quality medication, appropriate information on treatment schedules and effects of medication, as well as advice on the management of adverse events and use of complementary treatments.

## Introduction

Anita Waldmann

In recent years, substantial changes have been made to our approaches to healthcare provision. An increasing emphasis has been placed on a multidisciplinary approach to care, as well as treatment in the community setting. In addition, a substantial evolution in the way patients are involved in the management of their diseases (patient participation) has taken place. Many patients are keen to have an active say in their treatment and often look for additional material to supplement the information offered by their healthcare providers [1]. Indeed, a 'new consumer' has been described by pharmacists, predominantly young customers or the chronically ill, who are well informed, inquisitive, with a desire for longer dialogue and who ask critical questions and seek counselling [2]. Accordingly, the objective of patient management strategies has been defined to provide a patient-centred approach.

The pharmacist plays a key role both as a partner within the healthcare team, actively involved in the delivery of care through the provision of high quality medication on the one hand, as well as being a source of appropriate information and education regarding treatment schedules, desirable effects, as well as side effects of medication and including advice on the management of adverse events. This demonstrates a substantial maturation in the role of the pharmacist. In the future, pharmacists may also play a greater role in the independent prescribing of medicines [3].

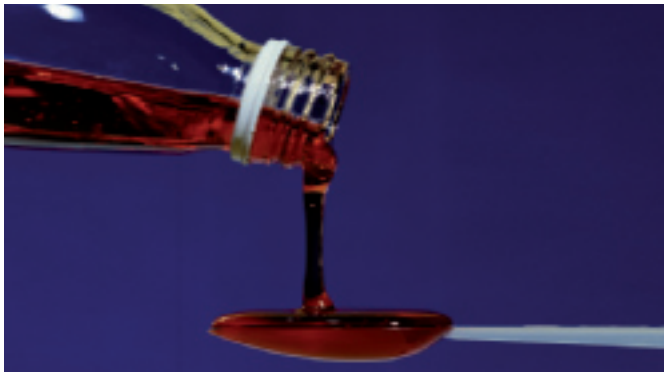
## Overview: patient expectations

Patients look to their pharmacist not as a salesperson, but as a skilled professional with up-to-date knowledge and expertise, to be able to offer appropriate advice and information both on general and specific health issues [4]. Key attributes of a pharmacist are respecting the privacy and confidentiality of patients, as well as offering compassion and empathy in discussions of their diseases, treatments or concerns, which highlights the importance of good communication and interpersonal skills [4-6]. Overall, in order to be beneficial, the relationship between pharmacists and patients needs to be built on mutual respect and trust.

The results of a survey by Worley et al. which investigated the views of patient and pharmacist concerning the expectations both patients and pharmacists have of each other are revealing in this respect [7]. The survey employed a questionnaire to collect information on the following aspects: information sharing, responsible behaviour, interpersonal communication, creating a patient-centred relationship, and active communication related to health care. The study revealed that both patients and pharmacists have similar views about the pharmacist's role in sharing information, such as how to look out for side effects and whether a co-administration of other medicines is feasible. However, patients agreed less on pharmacists' responsible behaviour, which specifically concerned working with patients to meet their health needs. In addition, patients agreed less about the pharmacist's role in creating a patient-centred relationship and interpersonal communications, which related to availability and approachability from a patient's point of view. Although these responses highlight aspects of the patient–pharmacist relationship that may benefit from improvements, the results, which were derived from national random samples in the US, may not be representative of the situation in Europe and, in addition, changes are likely to have occurred since the publication of this study in 2007.

## Providing appropriate information and advice

The amount of information following an initial diagnosis of a disorder can often be overwhelming and confusing for patients. In addition, the initiation of a new treatment, especially oral treatments, is accompanied by a host of questions and a thorough explanation of expected effects is invaluable. For many patients, the jargon used in package inserts can often be unclear and unsettling. In addition, patients may be reluctant about asking the treating physician for clarification. Here, pharmacists can play a key role in explaining relevant information and giving advice in plain language. This involves the clear communication of administration schedules, as well as effects of the treatment. In addition, pharmacists are able to provide tools to patients and their families to deal with side effects. A detailed explanation of possible symptoms and how these manifest themselves can greatly reassure patients and caregivers and reduce feelings of panic and powerlessness when they arise. Pharmacists can provide valuable education



regarding steps that patients themselves can take to manage side effects, as well as outlining signals that indicate serious side effects, which would require further advice and intervention from healthcare professionals. Provision of such management information will empower patients, greatly contributing to a responsible approach to therapy. Assessment of risks and ensuring their safety is a key concern for patients [5].

In summary, pharmacists play important roles as educators and counsellors on specific disease and treatments issues. In addition, there are chronic disorders, such as diabetes, for which patients' needs extend beyond advice on specific interventions to guidance on sustained lifestyle changes, an example that demonstrates the role of the pharmacist as an essential part of the interdisciplinary diabetes care team [8].

## Providing information regarding complementary medicines

Many patients are keen to supplement their treatments with complementary medicines, which they may not always disclose to their treating physician simply because they are not aware that negative drug interactions may arise [1]. Here, pharmacists can play a proactive and crucial role by asking about supplementary medicines and explaining the benefits, risks, and possible contraindications. Indeed, a survey conducted among Australian community pharmacies found that patients expect pharmacists to advise them on complementary medicines [1].

## Providing information regarding patient support organisations

Following the diagnosis of a serious or terminal illness, patients and families may feel isolated and confused and may benefit from contact with patients and caregivers in similar circumstances. Pharmacists are well placed to provide links or contact information for patient support organisations or other sources of information to assist patients and relatives with meeting other patients.

## Explanation of schedules and the importance of compliance

Medication schedules can be a source of confusion for patients, particularly if a number of medications have to be taken which require particular times or circumstances, e.g. fasting versus administration with food. Pharmacists play a key role in explaining schedules of administration, thereby reinforcing the information provided by the treating physician, as well as being in a good position to stress the importance of adherence to treatment schedules to maximise the effects of therapy [9].

Non-compliance is recognised to be a frequent problem in the outpatient setting [10] and a number of factors specifically contributing to non-compliance with antibiotic therapy have been identified. These include the cost of drugs, formulation, rapid improvement of symptoms, forgetfulness, frequent dosing, complex regimens, side effects and patient beliefs [10]. Non-compliance is associated with serious consequences, such as patients receiving inappropriate doses of medication, thereby affecting clinical outcomes. In addition, there are significant cost implications, not only because of wasted medications, but due to additional examinations and interventions that have to be implemented [10].

Through regular contact with patients or their family members, pharmacists are uniquely placed to discuss and review feasible and meaningful goals of therapy with patients to meet their expectations and ensure compliance to treatment.

## Conclusion

The role of the pharmacist has matured substantially over recent years to encompass not only the dispensing of medicine, but also a substantial involvement in disease management. Pharmacists play a key role in providing relevant information and advice on the practical aspects of treatment and are therefore essential partners in the multidisciplinary teams involved in the patient-centred provision of healthcare. The relationship between patients and pharmacists is therefore an integral aspect of ensuring patient welfare.

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## References

1. Braun LA, Tiralongo E, Wilkinson JM, Spitzer O, Bailey M, Poole S, et al. Perceptions, use and attitudes of pharmacy customers on complementary medicines and pharmacy practice. BMC Complement Altern Med. 2010;10:38.
2. Traulsen JM, Noerreslet M. The new consumer of medicine-the pharmacy technicians' perspective. Pharm World Sci. 2004;26(4):203-7.
3. Hobson RJ, Scott J, Sutton J. Pharmacists and nurses as independent prescribers: exploring the patient's perspective. Family Practice. 2010;27:110-20.
4. Tinelli M, Bond C, Blenkinsopp A, Jaffray M, Watson M, Hannaford P; Community Pharmacy Medicines Management Evaluation Team. Patient evaluation of a community pharmacy medications management service. Ann Pharmacother. 2007 Dec;41(12):1962-70.
5. Futter B. The naked patient. S Afr Pharm J. 2011;78(2):56.
6. Naik Panvelkar P, Armour C, Saini B. Community pharmacy-based asthma services-what do patients prefer? J Asthma. 2010;47(10): 1085-93.
7. Worley MM, Schommer JC, Brown LM, Hadsall RS, Ranelli PL, Stratton TP, et al. Pharmacists' and patients' roles in the pharmacist-patient relationship: are pharmacists and patients reading from the same relationship script? Res Social Adm Pharm. 2007;3(1):47-69.
8. Sisson E, Kuhn C. Pharmacist roles in the management of patients with type 2 diabetes. J Am Pharm Assoc. 2009;49(Suppl 1):S41-5.
9. Vivian EM. The pharmacist's role in maintaining adherence to insulin therapy in type 2 diabetes mellitus. Consult Pharm. 2007 Apr;22(4):320-32.
10. Kardas P, Bishai WR. Compliance in anti-infective medicine. Adv Stud Med. 2006;6(7C):S652-8.

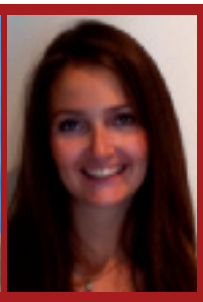
# Companion diagnostics and personalised cancer medicine

Cancer is a heterogeneous disease that requires an individualised treatment approach. Drug treatments guided by molecular diagnostic testing are increasingly being used in the clinic. This article shows that the concept of stratified cancer medicine has become a reality.

## Introduction

Our increased molecular understanding of human diseases will change the way that drugs are developed and how pharmacotherapy is practiced in the years to come [1, 2]. We know that most diseases are heterogeneous and that they can be divided into biological subgroups, each requiring a specific therapeutic intervention. When it comes to individualisation of pharmacotherapy, oncology has been at the forefront and a number of drugs have already been developed based on a detailed molecular knowledge of the disease mechanisms [3].

Jan Trøst Jørgensen MScPharm, PhD



Maria Hersom BSc

## Personalised and stratified medicine

When we talk about individualising pharmacotherapy we often use expressions like 'tailored therapy' or 'personalised medicine', which may give the impression of a totally individualised pharmacotherapy like 'targeting drugs for each unique genetic profile' [4]. However, this is yet far from being a reality. What we experience right now, and will continue to experience much more in the years to come, is that by using molecular diagnostic tests we will be able to divide the patients who 'share' molecular biological characteristics into subgroups and, based on this information, we can match these patients with the right drug. In this situation, the molecular diagnostics serve as a stratification test, which has led to the use of the expressions 'stratified medicine' or 'stratified pharmacotherapy'. Stratified medicine has been defined as follows: management of a group of patients with shared biological characteristics by using molecular diagnostic testing to select the most optimal therapy in order to achieve the best possible medicinal outcome for that group [5].

## Companion diagnostics

The molecular diagnostics tests used in stratified cancer medicine rely on different technologies and the dominating analytical methods are immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH), chromogenic *in situ* hybridisation (CISH), and reverse transcription-polymerase chain reaction (RT-PCR) [3]. When these molecular diagnostics tests are used in combination with drugs they have been given a specific name. Initially, these tests were called pharmacodiagnostics or theranostics, but within the last 3–5 years the expression 'companion diagnostics' has taken over. A companion diagnostics is defined as: a pre-treatment test performed in order to determine whether or not a patient is likely to respond to a given therapy. This type of test is classified as a predictive test and a prerequisite for implementation of stratified and personalised medicine [5].

A number of drugs are listed in Table 1 for the treatment of solid tumours where the clinical use is guided by a companion diagnostic test. For several of these drugs, it is a requirement that companion diagnostic testing is performed before they can be prescribed to the patient.

**Table 1: Drugs for the treatment of solid tumours where companion diagnostic tests are used**

| Drug | Indication | Biomarker |
|---|---|---|
| Tamoxifen (Nolvadex, AstraZeneca) | Breast cancer | ER |
| Letrozole (Femara, Novartis)<br>Anastrozole (Arimidex, AstraZeneca)<br>Exemestane (Aromasin, Pfizer) | Breast cancer | ER |
| Trastuzumab (Herceptin, Roche) | Breast cancer<br>Gastric cancer | HER2/*HER2*<br>HER2/*HER2* |
| Lapatinib (Tykerb, GlaxoSmithKline) | Breast cancer | HER2/*HER2* |
| Epirubicin (Ellence, Pfizer)<br>Doxorubicin (Adriamycin, Pfizer) | Breast cancer | TOP2A |
| Cetuximab (Erbitux, Bristol-Myers Squibb/Merck) | Colorectal cancer | EGFR/*KRAS* |
| Panitumumab (Vectibix, Amgen) | Colorectal cancer | EGFR/*KRAS* |
| Gefitinib (Iressa, AstraZeneca) | Non-small cell lung cancer | EGFR |
| Erlotinib (Tarceva, Roche) | Non-small cell lung cancer | EGFR |
| Imatinib (Glivec, Novartis) | Gastrointestinal stromal tumour | C-KIT (CD117) |
| Vemurafenib (Zelboraf, Plexxicon/Roche) | Melanoma | *BRAF V600E* |

## Stratified cancer medicine

Breast cancer, like most other cancers, is a disease where heterogeneity exists and where the principle of stratified medicine has in fact been practised for the last couple of decades. This already began in the 1970s with the development of the first selective oestrogen receptor

modulator tamoxifen. Tamoxifen was developed for women with oestrogen receptor positive breast cancer, which make up approximately 60–70% of the population with the disease [6]. From a phase II study with tamoxifen performed in patients with advanced breast cancer, published in 1976, it was concluded: a high degree of correlation between response and positive estrogen-receptor assay suggests the value of the diagnostic test as a means to select patients for tamoxifen treatment [7]. For the first time, we have a combination of a targeted drug and a predictive diagnostic assay/companion diagnostic test. Despite the fact that this study was published 35 years ago, the conclusion about combining drug and diagnostics seems more relevant than ever.

Late in the 1990s another example appeared, in fact the one which is most often referred in relation to personalised or stratified medicine, the combination of the IHC diagnostic test for HER2 and the monoclonal antibody trastuzumab. Trastuzumab targets the extracellular domain of HER2 and the effect is dependent on overexpression of the HER2 protein, or amplification of the *HER2* gene, which is tested for by IHC or FISH, respectively [3, 8]. These protein or gene changes occur in 20–25% of all women with breast cancer, and it is in this subset of patients that trastuzumab has shown to be effective [9, 10]. Recently, trastuzumab has also proven to be effective in advanced gastric cancer, especially in the subgroup of patients that had the highest overexpression of the HER2 protein [11]. When it comes to HER2 positive breast cancer, a number of monoclonal antibodies and tyrosine kinase inhibitors have been developed or are under development, such as lapatinib, neratinib (Pfizer), and pertuzumab (Roche/Genentech), so the treatment of this patient group may be even more effective in the future [12, 13].

Just as the development of trastuzumab must be regarded as a major breakthrough in the treatment of breast cancer, a new breakthrough seems to be under way in relation to the treatment of metastatic melanoma, where no effective treatment has so far been available. Very recently, promising interim phase III data with vemurafenib (Plexxicon/Roche) has been published [14]. Vemurafenib is a B-RAF kinase inhibitor that selectively blocks the RAF/MEK/ ERK pathway in *BRAF V600E* mutated cells [15]. It is estimated that approximately 40–60% of the melanoma patients have this type of BRAF mutation, which is measured by RT-PCR. In the phase III study vemurafenib was compared to dacarbazine in metastatic melanoma patients with the *BRAF V600E* mutation. The efficacy of vemurafenib was dramatically improved compared to dacarbazine, with a response rate of 48% for the patients treated with vemurafenib and only 5% for the dacarbazine group. The treatment with vemurafenib was further associated with a relative reduction of 64% in the risk of death and a 74% reduction in the risk of disease progression compared with dacarbazine [14]. This data must be considered a major step forward in the treatment of this highly deadly disease and it will be interesting to see what the effect will be on the median overall survival when the study is finally concluded. Based on the recent phase III data, the FDA has (on 17 August 2011) approved vemurafenib for the treatment of metastatic and unresectable melanomas together with the companion diagnostic test for *BRAF V600E* mutation.

## Conclusion

If medical anticancer treatment is to be improved, disease heterogenecity must be taken into account when drugs are developed and subsequently used in the clinic. The drug-diagnostic co-development model has already proven its value with drugs like tamoxifen, trastuzumab, imatinib, and now also with vemurafenib. The use of companion diagnostics will be a decisive factor in utilising the clinical potential of the new targeted anticancer drugs to the benefit of patients.

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## References

1. Jørgensen JT. From blockbuster medicine to personalized medicine. Per Med. 2008;5:55-63.
2. Collier R. Bye, bye blockbusters, hello niche busters. CMAJ. 2011;183(11):E697-8.
3. Jørgensen JT, Nielsen KV, Ejlertsen B. Pharmacodiagnostics and targeted therapies - a rational approach for individualizing medical anti-cancer therapy in breast cancer. Oncologist. 2007;12:397-405.
4. Langreth R, Waldholz M. New era of personalized medicine - targeting drugs for each unique genetic profile. Oncologist. 1999;4:426-7.
5. Jørgensen JT. Are we approaching the post blockbuster era? Pharmacodiagnostics and rational drug development. Expect Rev Mol Diagn. 2008;8(6):689-95.
6. Cheung KL. The estrogen and progesterone receptors - setting the scene for pharmacodiagnostics. In: Jørgensen JT, Winther H, editors. Molecular diagnostics - the key driver of personalized cancer medicine. Singapore: Pan Stanford Publishing; 2010. p. 21-42.
7. Lerner HJ, Band PR, Israel L, et al. Phase II study of tamoxifen: report of 74 patients with stage IV breast cancer. Cancer Treat Rep. 1976;60(10):1431-5.
8. Jørgensen JT, Møller S, Rasmussen BB, et al. High concordance between two companion diagnostics tests: a concordance study between the HercepTest and the HER2 FISH pharmDx Kit. Am J Clin Pathol. 2011;136: 145-51.
9. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar;344(11):783-92.
10. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol. 2011 Mar;12(3):236-44.
11. Jørgensen JT. Targeted HER2 treatment in advanced gastric cancer. Oncology. 2010;78(1):26-33.
12. Roy V, Perez EA. Beyond trastuzumab: small molecule tyrosine kinase inhibitors in HER-2 positive breast cancer. Oncologist. 2009;14(11):1061-9.
13. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. Cancer Res. 2008 Jul;68(14):5878-87.
14. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun;364(26):2507-16.
15. Bollaf G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010 Sep;467(7315):596-9.

# An assessment of the pharmacist's role in oncology trial management

This article reports on a ESOP survey which was undertaken to gather information about the current involvement of oncology pharmacists in clinical trial management across Europe. Significant differences in national practices are also highlighted and potential standardisation solutions are suggested.

## Introduction

Oncology is currently the fastest growing therapeutic area, and an increasing number of clinical trials are being conducted. Clinical trial management provides an excellent example of a multidisciplinary team approach. Indeed, the clinical research team will involve the sponsor, frequently its clinical research organisation (CRO) and development specialists, the principal investigator and doctors, clinical research assistants and possibly research nurse(s), pharmacists, laboratory technicians and perhaps social workers.

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The pharmacist has become an integral part of the clinical research team. As a drug expert, he is the right person to manage all of the trial's drug-related activities, thereby contributing to the overall smooth running of the study.

## Management of clinical trials in oncology

By participating in clinical trials in oncology, the clinical pharmacist contributes to quality assurance. QuapoS 4 provides a reference guideline to be used to organise pharmacist-driven activities that are related to clinical trials [1]. On the basis of all applicable legal regulations, services that the pharmacist could provide in a clinical trial setting are:

- investigational drugs ordering
- shipment reception
- storage
- adequate labelling according to EU legislation if not previously realised by the sponsor
- randomisation
- preparation of drugs, and eventual blinding
- dispensing
- return or disposal of used /unused investigational drugs.

Pharmacists may also become involved in studies that investigate a drug's stability, and the acceptance of patients who are selected to be enrolled on the clinical trial. Careful documentation of each of these steps in the clinical trial's file is mandatory.

## European survey

The role of pharmacy as a profession in the clinical research field needs to be fully understood. In recent years, European law has increasingly been implemented in national pharmaceutical law. However, practices can differ from one European country to another, as a result of differing legal regulations or historical pharmacy involvement. A study was therefore developed by ESOP to:

- gather information about the current involvement of oncology pharmacists in clinical trial management in Europe
- better clarify the level of pharmacy activities related to clinical trials in different European countries
- identify appropriate actions to improve current standings.

## Methodology

A short questionnaire was developed by three European pharmacists. All questions concerned pharmacist-related tasks during clinical trials, see Questionnaire. The questionnaire was circulated to all ESOP members with their online membership letter. It was also available on the ESOP website. Answers were collected from 21 December 2010 to 10 January 2011.

**Figure 1: Profile of hospital respondents**

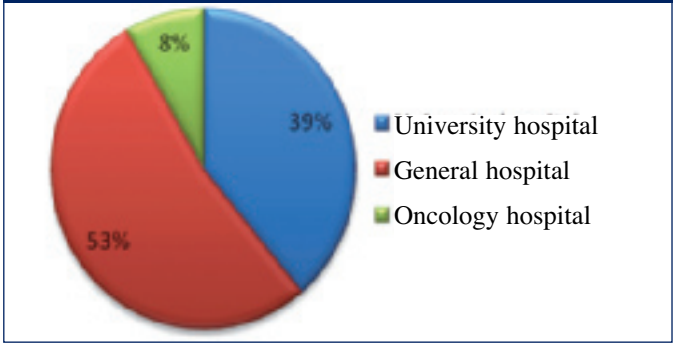
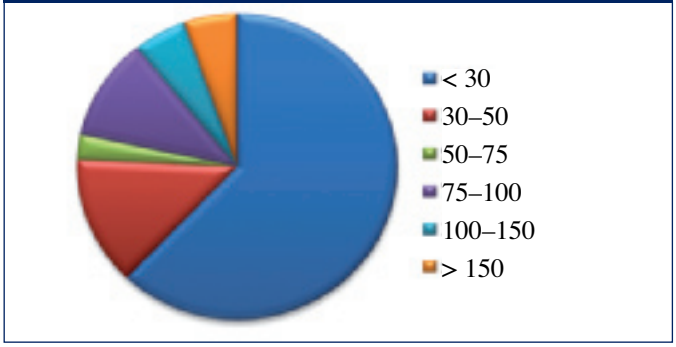



**Figure 2: Number of oncology clinical trials**



| Questionnaire |
|---|
| **Tasks:** medication/ancillaries order; cool chain medication transport verification; shipment delivery confirmation; temperature controlled medication storage; inventory review; medication preparation; billing; waste management including used medication containers destruction, expired medication destruction; communication with sponsor/CRO – monitoring visit, discrepancy reports, changes establishment; +/- subject randomisation; +/- medication reallocation. |
| 1. Name tasks different from the above mentioned that should/should not be your own. Does reality in your pharmacy overlap your opinion? |
| 2. Do you have independent 'Department for clinical trial management' or independent 'Employee for clinical trial management' in your pharmacy? If yes, what is its/his(her) scope (please specify in detail)? |
| 3. Do you have in your pharmacy transparent system of rewarding clinical trial staff according to its study workload? (In case you have independent 'Department for clinical trial management' or independent 'Employee for clinical trial management' in your pharmacy is it so all pharmacy employees are rewarded 'equally' taking into account their casual workload or those involved in clinical trial management are given an advantage over others?) |
| 4. Do you find better paper records or electronic ones (IVRS, IWRS)? Do you think they both have to be done or one is enough? Which one and why should then be preferred? |
| 5. Comparing clinical trial management with standard work do you think you need closer cooperation than just routine one with MDs (PI, subinvestigators) (please specify in detail)? |
| 6. When having a combination of orally medication and parenteral chemo in a single clinical trial do you in chemounits deal with orally medication as well or do you deal with parenteral chemo only and orally taken one is someone else responsibility (please specify in detail)? |
| This questionnaire is the original version produced by the authors.<br>PI: principal investigator. |

The completed questionnaires were returned by fax or were emailed as a PDF file.

## Results

The results from each question have been analysed separately in order to highlight any differences or similarities between each European country. However, they have been presented holistically here for simplicity. Collected data can only be taken as an illustration of the current situation for the responding pharmacy. It cannot be taken as representative of the current situation for each European country in general.

Thirty-seven completed questionnaires were received from 16 European countries. Germany had the highest proportion of respondents (40% of the total). Approximately half of the respondents worked in general hospitals, one-third were from university hospitals, and only 8% were from specialist oncology hospitals, see Figure 1. Most respondents (76%) had been involved with up to 50 clinical trials, see Figure 2.

**Table 1: Services provided by the pharmacy (% of respondents)**

| |
|---|
| **100%** |
| Cool chain medication transport verification |
| Shipment delivery confirmation |
| Temperature controlled medication storage |
| Medication preparation |
| **75–100%** |
| Inventory review |
| Communication with sponsor/CRO |
| Monitoring visit |
| Medication order |
| Waste management |
| Expired medication destruction |
| Expired/unused medication delivery to sponsor |
| Discrepancy report |
| **50–75%** |
| Co-management of all ongoing hospital clinical trials |
| Billing |
| Relabelling |
| Changes establishment |
| **25–50%** |
| Randomisation |
| Medication reallocation |
| Independent department for clinical trial management |
| Transparent rewarding system |

The pharmacy ward was involved in clinical trial management in 95% (n = 35) of the respondents' hospitals. Pharmacy technicians were involved in approximately half of the hospitals. The mean number of pharmacists per hospital involved in each trial was between two and three, and between three and four for pharmacy technicians.

Services provided by the pharmacy in relation to clinical trials are detailed in Table 1. There were few differences between countries, apart from relabelling, randomisation and medication reallocation. Billing was not systematic, and a transparent reward system was only reported by 25–50% of respondents. However, these relatively low figures do not mean that reward systems are generally absent. If the pharmacy staff are rewarded from the trial budget, the reward is shared equally without considering individual clinical trial management involvement.

Electronic records of data were usually preferred by respondents over paper records, especially interactive internet web response services (IWRS). However, both paper and electronic—IVRS (interactive voice response systems)/IWRS—were often required by the sponsor.

## Discussion and conclusion

Many oncology pharmacists currently operating in Europe

have extensive clinical trial management experience. This contribution has been widely recognised, with some tasks that have fallen to doctors now being allocated to the pharmacist. However, a transparent and equitable reward scheme for pharmacy-related tasks still needs to be standardised between countries. Communication between pharmacists and sponsors' clinical research assistants could also be improved with regard to specific pharmacy-related tasks, especially the preparation of new drugs. The application of European regulations, along with the implementation of QuapoS recommendations and the collaboration of European pharmacists should help to standardise practice.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## Reference

1. van Gemmern R. Quality standard for the oncology pharmacy services with commentary (QuapoS 4), 2008.

# Breast cancer irradiation: 2011 update

Several developments have recently emerged in the field of breast cancer radiotherapy. This article summarises those that most impact pharmacists.

Breast cancer radiotherapy is now established as a viable therapeutic strategy on a par with chemo- or hormone therapy. Principally, this is because lymph node-positive tumour irradiation not only reduces the frequency of tumour recurrence, but also improves overall survival. Modern irradiation technology is also now associated with fewer tolerability issues when compared with older radiotherapy techniques.

Professor Dr Wolfgang Wagner MD, PhD

There are also new recommendations regarding ductal carcinoma in situ (DCIS), specifically that radiotherapy is not necessary in the case of small malignant cells (< 2 cm), free resection margins (> 10 mm), and favourable gradings [1]. Furthermore, radiotherapy with N+/- status has a positive effect on overall survival and recurrence reduction after both mastectomy and breast-conservation surgery, see Figure 1 [2].

To date, physicians have been cautious when indicating radiotherapy in patients with breast reconstructions immediately following mastectomy. This is because of a fear of implant failure. A recent study by Ho et al. has indicated that under certain circumstances, early radiotherapy may be possible despite implants—the trial showed a rate of removal of implants/replacements of 21% after seven years [3].

The success of radiotherapy depends on the interval between surgery and the start of irradiation, a systematic review has suggested that this period should be a maximum of eight weeks, see Figure 2 [4]. Existing treatment programmes include primary chemotherapy, which can lead to a delay of

**Figure 1: Radiotherapy outcomes according to node status**

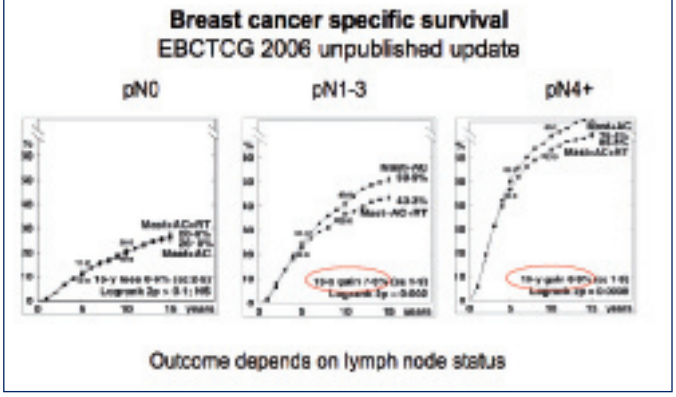



**Figure 2: Associations between delay in postoperative radiotherapy for breast cancer and local recurrence rates**

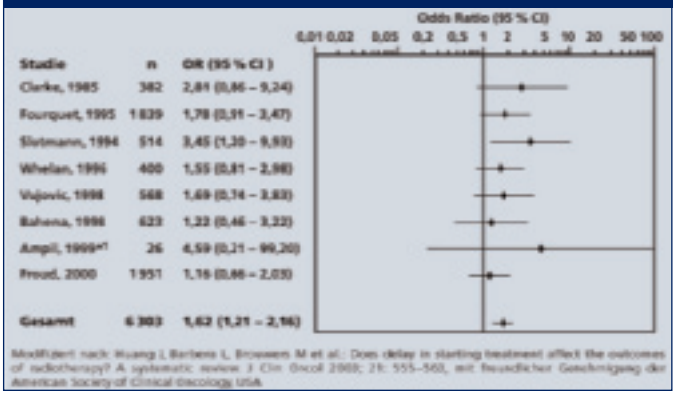
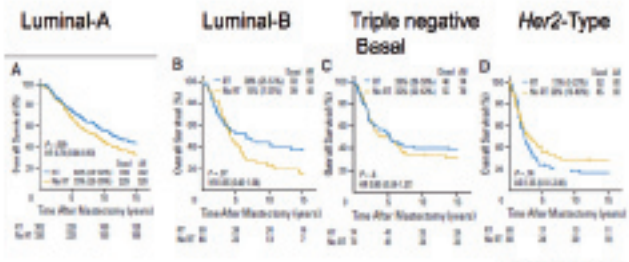


**Figure 3: Radiotherapy outcome versus tumour characteristics**




radiotherapy administration such that the risk of local recurrence is increased considerably, especially with regard to small tumour-free resection margins.

Partially accelerated breast irradiation—total dose given within one week—is not yet considered standard therapy, whilst intraoperative radiotherapy is still regarded as being in an experiemental phase. Follow-up currently spans only two years, meaning that results cannot be conclusively evaluated, even though the observed local tumour control is comparable with the established procedure and toxicity appears to be lower.

The results of radiotherapy depend on the tumour's molecular characteristics cf. chemotherapy. In fact, when certain molecular characteristics are present, radiotherapy can be a disadvantage for the patient, see Figure 3 [5].

## Conclusion

Breast cancer radiotherapy not only evokes local tumour control, but in certain circumstances, it can also extend overall survival. New irradiation technologies and programmes are likely to further improve results.

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## References

1. AGO Leitlinien 2010. AGO therapy guidelines 'Breast Cancer'. Guidelines for diagnosis and treatment of breast cancer (Empfehlung seit 2002). Available from: www.ago-online.org
2. McGale P, Darby S, Taylor C, Peto R. The 2006 worldwide overview of the effects of local treatments for early breast cancer on long-term outcome. Int J Radiat Oncol Biol Phys. 2006 Nov 1;66(3):S2-S3.
3. Ho AY, Cordeiro P, Wright J, et al. Favorable long-term outcomes are achievable in women with immediate permanent implant breast reconstruction and postmastectomy radiation. Int J Radiat Oncol Biol Phys. 2010 Nov 1;78(3):S3.
4. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol. 2003 Feb 1;21(3):555-63.
5. Kyndi M, Sørensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J, et al. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. J Clin Oncol. 2008 Mar 20;26(9):1419-26.

## Extravasation of cytotoxics: there is still room for improvement

### References (please see article on pages 18–19)

1. Mader I, Furst-Weger P, Mader RM, Nogler-Semenitz E, Wassertheurer S. Extravasation of cytotoxic agents, 2nd edition. Wien New York: Springer; 2010.
2. Parikh P, Pai VP, Ranjan S, Swami A, Cuchelkar V, Agarwal P, et al. Phlogenzym is safe and effective in reducing morbidity of vesicant chemotherapy extravasation - a prospective study. Int J Immunother. 2001; 17(2-4):163-70.
3. Langer SW, Sehested M, Jensen PB. Treatment of anthracycline extravasation with dexrazoxane. Clin Cancer Res. 2000;6:3680-6.
4. Laurie SW, Wilson KL, Kernahan DA, Bauer BS, Vistnes LM. Intravenous extravasation injuries: the effectiveness of hyaluronidase in their treatment. Ann Plast Surg. 1984;13:191-4.
5. Mouridsen HT, Langer SW, Buter J, Eidtmann H, Rosti G, de Wit M, et al. Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol. 2007; 18(3):546-50.
6. Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, et al. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. J Clin Oncol. 1995;13(11)2851-5.
7. Alley E, Green R, Schuchter L. Cutaneous toxicities of cancer therapy. Curr Opin Oncol. 2002;14:212-6.

## Hospital workers perceptions about nano-technology

### References (please see article on pages 35–36)

1. Siegrist M, Wiek A, Helland A, Kastenholz H. Risks and nanotechnology: the public is more concerned than experts and industry. Nat Nanotechnol. 2007 Feb 2 [cited 2011 Sep 28]. Available from: www.nature. com/naturenanotechnology
2. Toumey C. Rules of engagement. Nat Nanotechnol. 2007 Jul 2 [cited 2011 Sep 28]. Available from: www.nature.com/naturenanotechnology
3. Cobb M, Macoubrie J. Public perceptions about nanotechnology. Risks, benefits and trust. J Nanopart Res. 2004;6(4):395-405.
4. Scheufele D, Lewenstein B. The public and nanotechnology: how citizens make sense of emerging technologies. J Nanopart Res. 2005;7:659-67.
5. Currall SC. Nanotechnology and society new insights into public perceptions. Nat Nanotechnol. 2009 Feb 4 [cited 2011 Sep 28]. Available from: www.nature.com/naturenanotechnology
6. Miller CA, Cobb MD, Hays S. Public attitudes towards nanotechnology-enabled cognitive enhancement in the United States.
7. Getting to know the public. Nat Nanotechnol. 2009;4(2):71. [cited 2011 Sep 28]. Available from: www.nature.com/naturenanotechnology
8. Kahan DM, Braman D, Slovic P, Gastil J, Cohen G. Cultural cognition of the risks and benefits of nanotechnology. Nat Nanotechnol. 2009;4(2): 87-90.

# Extravasation of cytotoxics: there is still room for improvement

Ursula Pluschnig, MD; Shahla Farokhnia, aHPh; Gunar Stemer, aHPh; Professor Robert M Mader, DSc

As many patients receive more intravenous therapies than before, extravasation is a challenge that is here to stay for the foreseeable future. This article outlines several proposals for an improved quality management of these issues and discusses the science behind them.

## Introduction

Extravasation of vesicant cytotoxics still remains a major challenge. In contrast to many expectations, the use of classic cytotoxic agents has actually increased in the 'era' of targeted therapies. Patients, nowadays, frequently experience fourth- and fifth-line treatments and enjoy longer survival and a decrease in cancer mortality rates. Thus, an individual patient receives many more IV infusions than two decades ago. This fact explains why extravasation is not a fading memory, but a reality that is here to stay in the years to come. To face extravasations, this article does not summarise the management procedures already outlined extensively in several excellent reviews and books [1], but instead proposes actions aimed at quality management and to discuss open scientific issues, which need to be urgently addressed. These suggestions include establishing an 'Extravasation Task Force' in your hospital to deal with the implementation of quality control and knowledge management.

## Risk factors for extravasation

Several antineoplastic agents are associated with toxicity to cutaneous and subcutaneous tissue. The most common risk factors concern patient-associated and iatrogenic risk factors. With the hazard of irreversible complications after extravasation, prevention is of the utmost importance. A classification of antineoplastic agents addresses potential tissue damage: vesicant, irritant, and non-vesicant. Depending on the extravasated agent, a sequence of emergency measures need to be followed, which is best done by adhering to a standard operation procedure (SOP). There is good evidence for the successful use of antidotes for some antineoplastic agents. These antidotes are dimethylsulfoxide or hyaluronidase, often combined with topical measures such as cooling or application of heat, whereas the use of the anthracycline antidote dexrazoxane is still a matter of controversial discussion. Most relevant, novel compounds are poorly characterised regarding their toxic potential and are therefore to be considered as major drug-associated risks until clinical data are available.

## Building a task force in the institution

There are several good arguments to concentrate expertise and action in a task force:

- Splitting interventions between different departments and disciplines can result in contradictory measures and irreproducible management standards within one institution
- Hardly comparable documentation
- Expertise varies within departments that administer cytotoxics, e.g. oncologic wards versus clinical units that occasionally handle infusions of cytotoxics.

A possible approach is the formation of interdisciplinary clinical working groups with the following tasks:

1. Members of the task force are the first port of call within the hospital
2. Coordination of the subsequent treatment stages including the consultation of plastic surgeons
3. In regular meetings (similar to a tumour board) the group members discuss individual cases of extravasation with the aim to define SOPs
4. Training of hospital staff
5. Dissemination of results by publication of novel data.

Since the start of the task force at the Medical University of Vienna and the Vienna General Hospital in 2006, more than 200 cases have been managed proving its usefulness and allowing the accumulation of the necessary expertise in a large hospital within very few years. According to our experience, the working group should include members from the disciplines of oncology, plastic surgery, oncology pharmacy, clinical pharmacology, pathology, nursing, and (as required) physiotherapy. Given the pharmacological expertise of hospital pharmacists working in oncology, they may provide valuable contributions to extravasation management, when physicians and nursing staff are in urgent need of support. It is a rewarding opportunity to further engage in interdisciplinary clinical activities for the patient's benefit.

## Training staff members

Regular training sessions help to raise awareness in the institution's clinical members, medical, and nursing staff. Most importantly, they impart knowledge concerning a rapid, qualified, and appropriate intervention in a situation close to emergency.

## Documentation, documentation, documentation ...

Standardised documentation is crucial to follow and evaluate the measures taken, possible sequelae and the final outcome. It is good practice to use one of the available documentation sheets accessible via the Internet, e.g. www.paravasate.at, offering forms in both English and German. Documentation in the minimal version includes description of the event, symptoms, measures taken, sequelae, and aftercare.

## Knowledge management

Due to the lack of prospective clinical studies on extravasation of cytotoxic drugs, our current knowledge has to rely on individual case reports and animal studies. As this situation is not subject to change in the near future, creating evidence by adherence to SOP and stringent documentation is the hard way to overcome the current stagnation in this field.

## The science behind extravasation

The type of damage associated with cytotoxic agents is a central issue, becoming prominent with every new, registered substance. Even the relatively simple classification into three types of damage is sometimes difficult, let alone to propose more sophisticated sub-classifications, e.g. addressing the fact that the vesicant potential of paclitaxel is not comparable to that of anthracyclines.

After extravasation of vesicants, the clinical course and extent of damage can hardly be predicted. This is particularly true for anthracyclines, when necroses can develop even weeks after extravasation. Despite extensive pharmaceutical and pharmacological knowledge, there is no reliable method to predict tissue toxicity on the basis of physicochemical characteristics. Even when similar compound structures may be a helpful hint—as for the vinca alkaloids and the anthracyclines, clinical confirmation is always required.

As extravasations are not always noticed immediately, a time delay longer than five days often elapses [2]. This immediately raises the question of the time period allowed before the efficiency of antidotes is compromised. Established antidotes have been tested for their use immediately after the extravasation event. Dexrazoxane was active against anthracyclines for at least three hours after the extravasation event, but activity was clearly reduced for daunorubicin after six hours [3]. Even shorter time windows seem to apply for the antidote hyaluronidase [4]. For this reason, instruction of patients and regular monitoring of IV infusions is of such crucial importance: early detection enables us to use instruments when time is the most critical factor for effectiveness.

As dexrazoxane has been approved based on the data from two single-arm studies [5], it is not clear how its efficacy compares with that of the highly established clinical use of topical cooling dimethyl sulfoxide (DMSO), which has also been tested in a prospective clinical trial with a very similar rate of success [6]. This serious flaw in the study design makes it difficult to draw definite conclusions.

Pathological changes within the affected tissue have been poorly characterised so far. Although many authors know that inflammatory processes are not the primary event after extravasation, it would be very useful to understand the histopathological changes in the skin in order to limit the use of corticosteroids, which are still frequently administered without real evidence.

## New therapeutic entities

The pharmacological landscape has changed fundamentally over the last ten years and new oncology pharmacotherapy options will continue to emerge. With the introduction of mitosis-interfering compounds eribulin and vinflunin, two new chemical entities with novel mechanisms of actions, limited clinical experience and toxicological data enlarged the armamentarium of physicians. To date, few data regarding substance-specific risks and management procedures following extravasation exist. In the absence of conclusive data, the vesicant or irritant potential of new compounds can only be indirectly deduced from parameters such as structure-activity relationship and formulation characteristics (pH value, excipients, osmolarity of the infusion solution).

At the same time, new galenic formulations of well-established compounds, e.g. liposomal daunorubicin and doxorubicin, and protein-bound paclitaxel are increasingly used due to decreased local and systemic toxicity compared to their non-modified precursors.

Several monoclonal humanised antibodies, e.g. rituximab, trastuzumab, bevacizumab, cetuximab, panitumumab, and others, have become essential in the treatment of oncological and non-oncological diseases. So far, clinical experience has shown type 1 hypersensitivity reactions [7], which in rare cases result in severe side effects. Due to the mechanism of action, vesicant behaviour is highly unlikely, classifying them as low grade irritants. However, new humanised monoclonal antibodies, e.g. ipilimumab, brentuximab vedotin, emerge and for each individual compound the toxicity potential has to be evaluated again.

## Conclusion

In summary, extravasation remains a dreaded complication of cytotoxic chemotherapy, at least for the next decade. Healthcare professionals engaged in extravasation management have to be aware of uncertainties and a possible lack of data regarding tissue toxicity of new compounds. This lack of knowledge should be addressed by an interdisciplinary 'Extravasation Task Force' engaging in the regular assessment of compounds, screening of literature, management of extravasation and their sequelae, adequate documentation, and publishing relevant information for the concerned scientific community.

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## References

References can be found on page 17.

# DNA repair in cancer therapy: beneficial or harmful

A lot of research is being performed on the modulation of DNA repair and its exploitation as a therapeutic principle to enhance the effects of chemotherapy. This paper outlines chemotherapy-induced DNA damage, its repair, consequences and the current state of DNA repair inhibitor development.

## Introduction

Professor Dorothee C Dartsch PhD

DNA damage induced by endogenous and exogenous stimuli is a common event in every cell and its repair is routine because (as it is mandatory for cellular survival) efficient repair represents a strong survival advantage. The first report on DNA repair currently listed in MEDLINE dates from 1962 and describes the repair of UV-induced lesions. The knowledge that cells can recover from UV irradiation is even 30 years older than that. As there are a variety of different DNA lesions, cells have developed a matching variety of repair mechanisms some of which are interlinked and can serve as a backup for others if those happen to be 'out of order'. Most of these mechanisms were discovered in the 1960s and 1970s [1].

Classical DNA-targeting anticancer agents are just another source of DNA damage causing more lesions than usual during chemotherapy. Naturally, tumour and normal cells alike will attempt to repair the damage. Supposing that DNA repair enables cells to revert to their original state, repair in normal (stem) cells is a good thing because it reduces side effects, whereas in tumour cells it is unfavourable because it may help the cell to survive, which decreases the clinical response. However, there is increasing evidence that cells surviving DNA damage due to DNA repair do not necessarily maintain their genomic integrity, but instead sustain non-lethal mutations. If such a mutation conveys a growth advantage over other cells, it may give rise to a secondary tumour or to secondary resistance of the primary tumour.

## DNA repair pathways

DNA damage affects the bases, or the 'backbone' of DNA. Damage to the bases is repaired either directly by O6-methylguanine-DNA-methyltransferase (MGMT), mismatch repair (MMR), base excision repair (BER) or nucleotide excision repair (NER). A damaged backbone is equivalent to a DNA single or double strand break and is repaired by homologous recombination (HR) or non-homologous end-joining (NHEJ). For a recent review, see Pallis et al. [2].

The smallest alkyl residues, such as methyl and ethyl, are removed from the O6 position of guanine by MGMT which is also known as O6-alkylguanine DNA alkyltransferase (AGT). The modified guanine is directly reverted to its normal state, without the need to create and then fill a gap as with all other forms of DNA repair. Anticancer agents, such as temozolomide, pro- and dacarbazine, and nitrosoureas transfer small alkyl residues and may be more effective in the absence of MGMT.

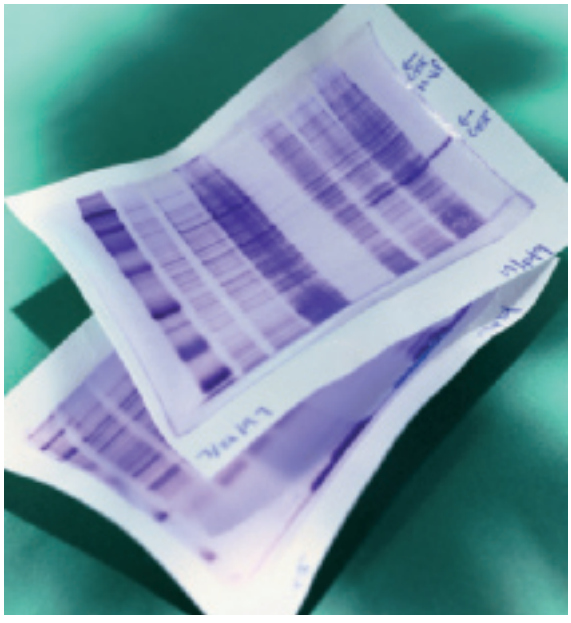
Bases modified by larger alkyl residues or oxidation are repaired by BER. The first step is the removal of the damaged base by a glycosylase, which leaves an intact backbone with an abasic site. Secondly, an apurinic or apyramidinic endonuclease cleaves the backbone and generates a strand break which is recognised by PARP. PARP enables binding of subsequent repair proteins such as polymerases and ligases. Synthesis of DNA along the intact strand is accomplished either by polymerase β, (can also be substituted by polymerase λ if only one base is replaced, or polymerases ε or δ that replace 2–13 bases. The overhanging flap of replaced DNA is removed by FEN1 (Rad27) before the XRCC1/ligase III complex joins the newly synthesised patch with the old strand.

If the chemical modification is even bigger, e.g. a bulky adduct or a thymidine dimer, the damage is repaired by NER. In regions of the genome that are not actively transcribed, the heterodimer of xeroderma pigmentosum (XP) protein C and hHR23B is required for damage recognition (global genome repair). Where active transcription occurs, transcription-coupled repair is not necessary to induce the next steps which are similar in both regions. The transcription factor IIH, replication protein (RPA) and a set of XP proteins (A, G, B, D, G, and F) cooperate to separate the two DNA strands at the damaged site, to stabilise the opening, and to excise 27–29 bases around the modified one. Subsequently, like in BER, polymerases ε or δ fill the gap and ligase III and/or ligase I join the strands.

Some forms of DNA damage, if unrepaired, can give rise to base mismatches and subsequent insertions and deletions during DNA replication. These are reverted by the MMR pathway. Recognition is accomplished by the protein MLH1 in varying heterodimeric combinations. The newly synthesised strand (identifiable by the lack of methylation) is incised and unwound by helicase. DNA exonuclease I excises the region around the mismatch, DNA polymerase δ fills the gap within the new strand and DNA ligase I seals the backbone.

The DNA double strand break is considered the most hazardous lesion because just one of them can cause cell death if

it persists into mitosis, or genomic rearrangements if mis-repaired. Two pathways have evolved that can accomplish repair of double strand breaks: HR and NHEJ. The pathway choice depends on different factors, e.g. cell type and cell cycle phase. In HR, recognition proteins named ATM and ATR recruit the ternary 'MRN-complex' that trims the 5'-ends at the break. This process is carried on by other enzymes and RPA binds to, and shelters, the generated single strand. In order to proceed with the repair, BRCA proteins 1 and 2 are needed to replace RPA with Rad 51. Binding of Rad 51 and/or XRCC 2 and 3 proteins leads to alignment of the broken with a homologous intact strand. The latter serves as a template to re-synthesise the broken strand. HR also serves to repair interstrand crosslinks and lesions generated at stalled replication forks. NHEJ requires damage recognition by Ku 70 and 80 proteins that bind to the ends of a break. They attract DNA-PKcs, an endonuclease that trims the ends of the broken strands and recruits polymerases λ and μ as well as DNA ligase IV that serve to fill the gaps and reseal the DNA backbones. An alternative form of NHEJ relies on PARP and the MRN complex to accomplish a limited resection of DNA ends at microhomology regions. Repair work is finished by the XRCC 1/ligase III complex. Thus, the alternative NHEJ pathway shares some key players with BER.



Mutations in genes coding for DNA damage response-associated proteins are well known to cause severe disorders like ataxia telangiectasia, xeroderma pigmentosum, hereditary non-polyposis colorectal carcinoma, Bloom's syndrome, BRCA-associated breast and ovarian cancers, and Fanconi anaemia.

## Chromosomal rearrangements and secondary malignancies

Important knowledge about the long-term effects of anticancer chemotherapy comes from studies such as the British Childhood Cancer Survivor Study and the Childhood Cancer Survivor Study performed in the US and Canada. The first has followed, and is still following, a cohort of 17,981 five-year survivors of childhood cancer diagnosed with cancer at younger than 15 years between 1940 and 1991 in Great Britain (for the most recent publication see [3]). The second is a follow-up of 14,358 similar patients diagnosed between 1970 and 1986 in the US and Canada (for the most recent publication see [4]). Of the childhood cancer survivors within these two studies, 7.4% in the British and 9.6% in the American study had a diagnosis of a secondary neoplasm, which implies a cancer risk about four times higher than in the average, non-childhood cancer population after a median follow-up time of 24.3 and 23.0 years from diagnosis, respectively. The most common secondary tumour entities (in descending order) were central nervous system (CNS) tumours (mainly gliomas), non-malignant skin cancer, gastrointestinal, genito-urinary, breast, and bone cancers in the British study and non-malignant skin cancer, breast, thyroid, CNS cancer, sarcoma, bone cancer and leukaemia in the American study [5]. Moreover, data from those patients who survive the first have a very high risk of developing further, secondary neoplasms. Among the British cancer survivors with a secondary neoplasm, most had been treated for the primary tumour with alkylants or anthracyclines, some with epipodophyllotoxins or platinum agents, and sometimes as combined radiochemotherapy. The distribution of primary anticancer therapies was similar in the American study, as can be deduced from the freely accessible study data (ccss.stjude.org).

Other studies have revealed that secondary malignancies are characterised by distinct genetic rearrangements. One example is the study from Aguilera et al. who reported that, of 22 children with therapy-related myelodysplastic syndrome/acute myeloid leukaemia, none had normal cytogenetics [6]. The most frequent alteration was a del(7) genotype (all of these patients had received prior therapy with alkylating agents) and a t(9;11) genotype (all patients had received etoposide). On the other hand, patients treated with alkylating agents frequently show a set of unbalanced genetic aberrations: the loss of the whole chromosomes 5 and/or 7 (-5/-7 genotype) or the gain of a whole chromosome 8 (+8 genotype) [7]. Thus, one might suspect that mutagenic anticancer agents leave a 'fingerprint' of typical genetic alterations.

But how can there be characteristic translocations after the non-specific DNA damage inflicted by cytostatic compounds? To date, there are only vague hypotheses to explain this: the majority of random rearrangements may involve essential genes and, therefore, be lethal, which means that we do not see tumours with such rearrangements. Some agents have, if not a specific, then at least, a preferential site to cause damage, like the cleavage sites of topoisomerase II. The nuclear architecture may play a role in that it determines the proximity of certain chromosome bands and co-localisation with chromatin structural elements, e.g. topoisomerase II, scaffold attachment regions, regions of chromatin that are unprotected by histones and thus accessible for the transcription machinery and other enzymes working on DNA. Finally, an NHEJ signature has been found for all translocations known so far that consists of small deletions and duplications

in each breakpoint, micro-homologies and non-template insertions [8].

## DNA repair inhibition as a therapeutic principle

It is probably too simplistic to assume that DNA repair guarantees cellular survival, as we and others were able to show that (at least *in vitro*) cells still die despite DNA repair [9-11]. Nevertheless, more and more studies suggest that it may be worthwhile to consider the effectiveness of the different repair pathways in order to guide the choice of the anticancer agent. For example, it has been shown that patients with a silent MGMT pathway benefit more from temozolomide, those with a low ERCC 1 level (NER pathway) from cisplatin, and those with an MMR defect from irinotecan, as opposed to patients with functioning repair pathways [12]. It is only a stone's throw from this recognition to the idea that DNA repair might be systematically modulated in order to improve the effectiveness of chemotherapy.

Inhibition of DNA repair, concomitant with a DNA-targeting chemotherapy is a compelling concept, not least because it may even possess some tumour specificity. Many tumours are characterised by abnormal DNA repair pathways. Thus, if there are two pathways A and B for a given DNA lesion and a tumour cell has a loss-of-function mutation for pathway A, it will be very vulnerable to DNA damage in the presence of an inhibitor of DNA repair pathway B, in contrast to a normal cell with two functioning repair pathways. This concept is called 'synthetic lethality', and it is currently exploited mainly in BRCA 1/2 defective tumours. For a recent review see [13]. This defect occurs frequently in hereditary forms of breast and ovarian carcinoma, but also in some sporadic tumours, such as triple negative (i.e. estrogen receptor (ER), progesterone receptor (PR) and HER2 negative) breast cancer. Cells with a BRCA 1/2 defect are over-reliant on PARP to initiate repair at double strand breaks generated by stalled replication forks. Inhibition of PARP in these cells has been shown to augment the effect of anticancer agents. These findings have prompted researchers and companies to further develop DNA repair inhibitors.

The group of DNA repair inhibitors that is furthest along the road towards the market are inhibitors of a repair enzyme called poly(ADP-ribose) polymerase, PARP. The three early ones are iniparib, olaparib, and veliparib, which are now in phase III clinical studies. The PARP inhibitors tested so far have shown fair tolerability alone and in combination with chemotherapy. However, initial euphoria about the new and promising target has been followed by some disappointment concerning iniparib because a phase III trial with more than 500 patients with triple negative breast cancer did not match the hopes kindled by earlier studies [14]. This does not, however, eliminate the class of PARP and other DNA repair inhibitors from the list of promising, new biological response modifiers. For one thing, iniparib is probably the weakest of the inhibitors, for another, it may still be effective in specific subsets of patients with breast cancer and/or patients with other tumours that were not adequately represented in the study. Furthermore, PARP is not the only interesting target among the DNA repair proteins. Research is currently addressing other proteins like MGMT, the CHK1 and 2, ATM and ATR kinases, Rad 51, and probably many more.

A very relevant question will be the long-term safety of treatment with any DNA repair inhibitor. Naturally, this is a completely black box at the moment, and it will take many years to find the answers, as we know from long-term studies with classical antineoplastic agents.

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## References

1. Ljungman DG, et al. The DNA damage response: repair or despair? Environ Mol Mutagen. 2010;51:879-89.
2. Pallis AG, et al. DNA repair pathways and their implication in cancer treatment. Cancer Metastasis Rev. 2010;29:677-85.
3. Reulen RC. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA. 2011;305(22):2311-9.
4. Armstrong GT, et al. Occurrence of multiple subsequent neoplasms in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 29:3056-64.
5. Meadows AT, et al. Second neoplasms in survivors of childhood cancer: findings from the childhood cancer survivor study cohort. J Clin Oncol. 2009;27:2356-62.
6. Aguilera DG, et al. Pediatric therapy-related myelodysplastic syndrome/acute myeloid leukemia: the MD Anderson Cancer Center Experience. J Pediatr Hematol Oncol. 2009;31(11):803-11.
7. Pedersen-Bjergaard, et al. Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia. 2008;22:240-8.
8. Schiavetti A, et al. Two secondary leukemias among 15 children given oral etoposide. Med Pediatr Oncol. 2001;37(2):148-9.
9. Dartsch DC, et al. Repair of idarubicin-induced DNA damage: a cause of resistance? DNA Repair. 2007;6(11):1618-28.
10. Schonn I, et al. Cellular responses to etoposide: cell death despite cell cycle arrest and repair of DNA damage. Apoptosis. 2010 Feb;15(2): 162-72.
11. Schonn I, et al. Ku70 and Rad51 vary in their importance for the repair of doxorubicin- versus etoposide-induced DNA damage. Apoptosis. 2011;16:359-69.
12. Martin SA, et al. Genomic instability and the selection of treatments for cancer. J Pathol. 2010; 220(2):281-9.
13. Shaheen M, et al. Synthetic lethality: exploiting the addiction of cancer to DNA repair. Blood. 2011:117(23):6074-82.
14. Sanofi-aventis reports top-line results from phase III study with BSI-201 in metastatic triple-negative breast cancer [press release]. Sanofi-aventis; 2011 Jan 27. [cited 2011 October 21]. Available from: http://en.sanofi.com/Images/13666_20110127_BSI_en.pdf

# Cold water reconstitution of Vidaza® with subsequent refrigerated storage prolongs drug stability

Anthony Tutino[1], RPh; Mei Lai[1,2], PhD


## Abstract

**Study Objectives:** This study assessed whether the stability of azacitidine suspension can be prolonged when reconstituted with refrigerated water for injection followed by storage under refrigerated conditions.

**Methods:** Two lots of azacitidine (Vidaza) were reconstituted with refrigerated (2–8ºC) water for injection to form a suspension and immediately stored refrigerated (2–8ºC). After storage for 16, 18, 20, or 22 hours, azacitidine suspension was then placed at a constant 25ºC for 30 minutes then tested for potency, redispersibility time, and suspension appearance. Sterility testing was performed at the end of the study. Stability of azacitidine was defined as maintaining > 90% potency.

Results: Azacitidine reconstituted with cold water (2–8ºC) followed by refrigerated storage (2–8ºC) and 30 minutes equilibration to 25ºC remained stable from baseline to 22 hours with a maximum loss of potency of 2.7% for each of the two lots of drug evaluated. At the 16, 18, 20, and 22 hour study time points and 30 minutes equilibration to 25ºC, redispersion time was 0.3 minutes with the appearance of fine white particles in suspension. All reconstituted vials stored refrigerated (2–8ºC) passed sterility testing at the end of study. Reconstitution of azacitidine with cold water for injection together with subsequent refrigerated storage is associated with a threefold prolongation in the stability time of the drug from 8 to 22 hours.

**Conclusion:** This substantial increase in the time of azacitidine maintaining > 90% potency allows for prolonged in-use time that may provide for more convenience for pharmacists.


**Keywords:** Azacitidine, cold water, reconstitution, stability, Vidaza

## Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid haematologic disorders characterised by aberrant, clonal haematopoietic stem cells producing abnormal red blood cells, platelets, and neutrophils. These abnormal cells never fully mature and lead to cytopenias with patient sequelae of severe anaemia as well as fatal bleeding and infections. There is also the risk of transformation to acute myeloid leukaemia in MDS. Myelodysplastic syndromes is a disease of the elderly. Thus, as people's lifespan has increased, the incidence and prevalence of MDS has risen over the last several decades. In Europe and North America, the median age of MDS patients at presentation is 76 years. Moreover, the incidence of MDS increases with age with the annual incidence rising from 15 to 50 cases per 100,000/year in those aged 70 years and older [1].

Azacitidine (Vidaza®, Celgene Corporation, Summit, NJ, USA) is a cytidine nucleoside analogue and inhibitor of DNA methyltransferase [2-3], approved in the EU for treatment of higher-risk MDS, chronic myelomonocytic leukaemia (CMML, 10–29% marrow blasts without myeloproliferative disorder), and WHO-defined acute myeloid leukaemia with 20% to 30% blasts and multi-lineage dysplasia. Azacitidine has demonstrated the ability to prolong overall survival in patients with higher-risk MDS compared with conventional care [4].

Azacitidine is rapidly degraded in water by hydrolysis [2-3]. Thus, per current EU Marketing Authorisation, azacitidine is to be reconstituted with sterile water for injection (WFI) to form a suspension and then administered within 45 minutes if stored at 25ºC. After reconstitution with sterile WFI, azacitidine suspension may be refrigerated (2–8ºC) for up to 8 hours. Reconstituted under these conditions and times, azacitidine has been shown to remain stable (> 90% potency). However, recent evidence suggests that the drug degradation of azacitidine may be slowed with a decrease in temperature of the WFI used for reconstitution. The purpose of this study was to assess whether reconstituting azacitidine with refrigerated WFI (2–8ºC) followed by refrigerated storage at 2–8ºC would prolong the drug stability time of azacitidine.

## Analytical methods and stability testing

The potency of azacitidine was determined by quantitating the sample against an external standard utilizing reverse phase chromatography with UV detection. This method has been fully validated in accordance with ICH Guidance Q2 (R1) [5]. The determination of suspension appearance for redispersibility time was performed visually, in accordance with ICH guidelines [6]. All of the analytical methods have been registered and accepted by the EMA for the testing of azacitidine.

Stability testing of azacitidine was performed by utilising validated regulatory accepted analytical methods in accordance with ICH guidelines [7]. These studies have been conducted at conditions which encompass long-term, intermediate and accelerated storage of the drug product over a period of time. The results of these stability studies on azacitidine have demonstrated product stability and have been acknowledged by the EMA.

## Materials and methods

Two lots of sterile commercial scale azacitidine drug product, each nearing the end of their expiry period of 48 months, were used for the study. Each lot of drug product was prepared as a homogeneous mixture of lyophilized powder and placed in

**Table 1: Averaged* Azacitidine assay† Stability‡ after cold WFI reconstitution and refrigerated storage (2–8°C) from baseline (0 hours) to 22 hours**

| | Baseline for 3 vials* | Average % assay at BL | 16 hours for 3 vials* | Average % assay at 16 hours | 18 hours for 3 vials* | Average % assay at 18 hours | 20 hours for 3 vials* | Average % assay at 20 hours | 22 hours for 3 vials* | Average % assay at 22 hours |
|---|---|---|---|---|---|---|---|---|---|---|
| **Lot 1** | | | | | | | | | | |
| Assay | 95.3%<br>94.6%<br>96.7% | 95.5% | 93.7%<br>94.3%<br>93.7% | 93.9% | 94.2%<br>93.2%<br>93.6% | 93.6% | 91.6%<br>93.0%<br>92.9% | 92.5% | 92.5%<br>92.9%<br>93.0% | 92.8% |
| % loss of assay from BL | | – | | 1.6% | | 1.9% | | 3.0% | | 2.7% |
| **Lot 2** | | | | | | | | | | |
| Assay | 95.2%<br>94.5%<br>95.9% | 95.2% | 94.6%<br>93.2%<br>93.3% | 93.7% | 93.6%<br>93.3%<br>91.1% | 92.7% | 92.8%<br>92.6%<br>93.4% | 92.9% | 93.7%<br>91.9%<br>91.9% | 92.5% |
| % loss of assay from BL | | – | | 1.5% | | 2.5% | | 2.3% | | 2.7% |

*Each averaged per cent comes from 3 vials of product; †% per EU Marketing Authorisation; ‡Stability of Vidaza based on maintenance of > 90% potency. WFI, water for injection.

labelled vials in preparation for reconstitution. Vials from each lot of azacitidine drug product were then reconstituted with 4 mL of refrigerated (2–8ºC) WFI and immediately placed in refrigerated storage (2–8ºC). After refrigerated storage for 16, 18, 20, and 22 hours, reconstituted vials of azacitidine were removed from refrigeration and placed at 25ºC for 30 minutes. Equilibration time to 25ºC for refrigerated azacitidine suspension has been previously determined to be 30 minutes per EU Marketing Authorisation. After 16, 18, 20, and 22 hours of refrigerated storage and 30 minutes equilibration to 25ºC, the reconstituted vials were shaken vigorously and tested for potency, redispersibility time, and appearance of the suspension. Stability of azacitidine was defined as maintaining > 90% potency. Sterility of the refrigerated drug product was assessed for reconstituted vials stored at 2–8ºC at end of study.

## Results

After cold water (2–8ºC) reconstitution and refrigerated storage (2–8ºC) followed by 30 minutes equilibration to 25ºC, azacitidine remained stable from baseline to 22 hours with a maximum loss of potency of 2.7% for each of the 2 lots of drug product evaluated, see Table 1. At the 16, 18, 20, and 22 hour study time points and 30 minutes equilibration to 25ºC, redispersion time was 0.3 minutes with the appearance of fine white particles in suspension and the absence of clumps. All reconstituted vials stored refrigerated (2–8ºC) passed sterility testing at end of study.

## Discussion

Because azacitidine readily degrades in water after reconstitution, the drug—per the EU Marketing Authorisation—must be administered within 45 minutes when stored at 25ºC and within 8 hours under refrigerated conditions to assure maintenance of potency of > 90%. The results of this trial, however, show that the stability (> 90% potency) and usage time of reconstituted azacitidine can be prolonged nearly threefold from 8 hours to 22 hours using cold water (2–8ºC) reconstitution followed by refrigerated (2–8ºC) storage. This reconstitution procedure showed no effects on redispersibility, appearance, or sterility after the prolonged refrigerated storage time. These findings have important implications for providing expanded usage time with azacitidine for pharmacists and other caregivers.

## Conclusion

Reconstitution using cold WFI followed by refrigerated storage is associated with a threefold prolongation in the stability time of azacitidine (8 to 22 hours). This substantial increase in the time of azacitidine maintaining > 90% potency allows for prolonged in-use time that may provide for more convenience for pharmacists.

## Acknowledgements

The authors wish to acknowledge the assistance of Acceleration Laboratory Services, Inc, 2634 NE Hagan Road, Lee's Summit, MO 64064, USA, in the conduct of this study and the writing assistance of Mr Neil Malone, MA, of Celgene Corporation, in the development of this manuscript.

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## References

References can be found on page 34.

# A practical approach to oral tumour therapy

Oral anti-tumour drugs present many challenges for medical staff, pharmacists, and patients [1]. A recent German Society for Oncological Pharmacy (DGOP) initiative sought to address some of the more urgent questions in this complex field [2]. This article summarises the collaborative thoughts of a haemato-oncologist and a pharmacist.

## The problem

Jürgen Barth

Oral anti-tumour drugs are commonly considered to be less aggressive, less toxic, and less problematic than their IV counterparts. However, despite the long-term availability of some of these agents, there is no recent guidance regarding the administration of these drugs. In order to achieve optimal patient outcomes, it is vital that information is constantly updated. This helps to ensure that well established compounds such as busulfan or cyclophosphamid, and fairly new targeted therapies such as imatinib and everolimus, continue to be used optimally. Some of the most commonly available oral tumour therapies are listed in Table 1.

This article focuses on small (low) molecular (weight) kinase inhibitors (SMKIs), considered by many experts to be the 'rising stars' of personalised targeted therapy. SMKIs are considered to be highly selective against tumour cells, but they can also have severe, sometimes life-threatening side effects. Their toxicities affect most organs, and include carcinogenic, mutagenic, and toxic to reproduction effects. These toxicities result from inhibiting not only tumour-dependent kinases in the tumour cells, but also the normal variant counterparts in healthy cells, exactly as classical chemotherapy affects both the tumour and host organism.

## Compliance

Oral (chemo-) therapy relies heavily on patient compliance. Physicians and nurses must therefore work together to explain the therapy to the patient, and counter any individual fears and side effects. Oral therapy may lead to an increased quality of life and greater self-management, but if this type of therapy is mismanaged, it can evoke serious side effects and become burdensome.

## Food

The bioavailabilities of oral cytostatics vary extensively, depending on the timing of concomitant food intake. The effect of fat or other food components may result in over or underdosing, depending on the exact drug administered. Table 2 provides an overview of recommended oral SMKI administrative timing in relation to food intake.

## Knowledge

Patients need to know the advantages and disadvantages of their therapy, their exact dosing requirements, and why they should not discontinue therapy. To achieve these objectives, doctors and pharmacists must work together, the therapy must be practical enough to fit in with the patient's daily routine, and the patient must be informed of the exact circumstances when he/she should contact his/her physician. During the patient consultation, however time-consuming or demanding it may turn out to be, it is essential to ensure that the patient agrees to the therapy and that the information provided is not intimidating, overwhelming, or complicated.

## Interactions

Concomitant intake of medicines with food and/or other drugs may result in unwanted interactions between the cytochrome P450 superfamily of metabolic enzymes. However, these interactions only become important if they result in a clinically significant effect, e.g. an inhibition of degradation that causes a 2- to 5-fold difference in predicted plasma levels. Like approximately 50% of therapeutic entities, SMKIs are metabolised by *CYP3A4*. When two molecules are simultaneously metabolised by *CYP3A4*, it is difficult to predict which one will take precedence. As a practical approach, all medicines and supportive agents such as vitamin or mineral tablets must be reported, the patient must be informed of any potential inter-

**Table 1: Classes and INN names of oral anti-tumour therapeutics**

| Alkylating agents | Antimetabolites | Podophyllotoxine derivatives | IMIDs | SMKI |
|---|---|---|---|---|
| Busulfan | Capecitabine | Etoposide | Lenalidomide | Dasatinib |
| Chlorambucil | Fludarabinphosphate | Topoisomerase I inhibitor | Pomalidomide* | Erlotinib |
| Cyclophosphamide | Methotrexate | Topotecan | Thalidomide | Everolimus |
| Estramustine | Mercaptopurine | Topoisomerase II inhibitor | | Gefitinib |
| Lomustine | S 1 | Idarubicin | | Imatinib |
| Melphalan | Tegafur-uracil | Vinca-alkaloides | | Lapatinib |
| Procarbazine | Tioguanine | Vinorelbine | | Nilotinib |
| Temozolomide | | Other | | Pazopanib |
| Treosulfan | | Hydroxycarbamid | | Sorafenib |
| Trofosfamide | | Mitotane | | Sunitinib |
| | | Hormone/anti-hormones | | Vandetanib |

IMIDs: immune modulatory drugs; *Pomalidomide not yet approved.

actions, and if applicable he/she must refrain from their concomitant medication.

**Table 2: Recommended SMKI administration in relation to food intake**

| To be taken with food | To be taken without food | No matter |
|---|---|---|
| Imatinib | Erlotinib<br>Everolimus<br>Lapatinib<br>Nilotinib<br>Pazopanib<br>Sorafenib | Dasatinib<br>Gefitinib<br>Sunitinib<br>Vandetanib |

## Side effects and toxicity management

SMKIs that target the epidermal growth factor receptor (EGFR) and the anti-EGFR-monoclonal antibodies, also act against the EGFR in normal skin. This can evoke dermatotoxicities such as inflammation and acne-like efflorescence, without the bacterial infection. Firstly, the skin changes in a way similar to acne, then it becomes dry, and finally it is rendered very sensitive and dry. There are many recommendations available for reversing all of these three phases [3-5].

There is some evidence to suggest that RAF-kinase inhibitors may evoke secondary malignancies such as carcinoma of the epithelium [6]. As a consequence, pharmacists, physicians, and nurses should monitor closely any changes in the patient's skin.

SMKI inhibition can also adversely affect several healthy kinase variants in the heart [7]. The fusion protein BCR/Abl is the molecular driver of chronic myeloid leukaemia, and because dasatinib, imatinib and nilotinib not only inhibit BCR/Abl but also the unmutated form of the Abelson-kinase that is essential for cardiomyocyte survival, heart function can become diminished. Off-target cardiotoxicity has also been reported with other SMKIs, including *RSK*, *RAF*, and *HER2*. As a consequence, heart function should be monitored for the duration of SMKI therapy. This includes the monitoring of QT changes, a sign of arrhythmia.

Other organs that can be affected by SMKI toxicity are the thyroid gland (sunitinib, pazopanib) and the liver [8]. Blood pressure is influenced by all anti-angiogenic agents, e.g. vascular endothelial growth factor inhibitors, and routine blood pressure monitoring is therefore necessary. Class effects include hypertension and venous thrombosis.

## Gastrointestinal toxicity

All known ATP mimetics cause (sometimes dose-limiting) diarrhoea, and some degree of nausea and vomiting. Many patients seem uneasy talking about diarrhoea. Initially, patients need to understand the definition of diarrhoea. Grades of diarrhoea are clearly defined in the Common Terminology Criteria for Adverse Events version 4.0, 28 May 2009, by the number of stools per day, and if applicable, ostomy output. Intervention can include the use of loperamide. Ciprofloxazin use is mandatory if diarrhoea persists for more than 48 hours. Octreotid can be regarded as rescue medication if symptoms continue to persist.

## Conclusions

- Close collaboration between the physician, nurse and pharmacist is essential for guiding the patient through oral chemotherapy.
- Medical and pharmaceutical staff should be highly educated about oral anti-tumour therapies.
- Prescriptions should always be dispensed on time.
- Physicians and pharmacists should share patient information and ensure that it is as helpful as possible.
- Oral tumour therapy is complex, and all healthcare stakeholders should work together.
- Confidence and clarity are mandatory when advising patients about the importance of compliance.
- All recommended supportive medications should be closely scrutinised, and should be chosen after careful consideration of the patient's individual situation—an inability to do so may be counter-productive.

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## References

1. Barth J. Kompetente Antworten auf scheinbar leichte Fragen. Onkologische Pharmazie. 2009;11(3):4-7.
2. Deutsche Gesellschaft für Onkologische Pharmazie (DGOP). Orale Zytostatikatherapie — sicher und effektiv durch gemeinsame Beratung. Available from: www.dgop.org/anmeldung_kampagne.php
3. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;(10):803-12.
4. Potthoff KM, Hassel JC, Wollenberg A, et al. Therapie und Prophylaxe EGFR-Inhibitor-induzierter Hautreaktionen. Arzneimitteltherapie. 2010; 28:191-8.
5. Schimanski CC, et al. Cetuximab-induced skin exanthema: Improvement by a reactive skin therapy. Mol Med Report. 2010;3(5):789-93.
6. Dubauskas Z, et al. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. Clin Genitourin Cancer. 2009;7(1):20-3.
7. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer. 2007;7(5):332-44.
8. Loriot Y, et al. Drug insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy. Nat Clin Pract Oncol. 2008;5(5):268-78.

# Setting up a pharmacist-led chemotherapy clinic: a practical guide

In the UK, several pharmacist-led chemotherapy clinics have been reported. The increasing use of oral chemotherapy is revolutionising the way that chemotherapy services are provided. This article is a practical guide for oncology pharmacists who are considering setting up a chemotherapy clinic.

## Introduction

In the UK, pharmacists and nurses have been able to train as prescribers since 2003. Initially, this was in partnership with a doctor (called supplementary prescribing), but more recently, pharmacists have been able to prescribe independently. Under current legislation, trained pharmacists can prescribe the full range of licensed and unlicensed medicines, with the exception of controlled drugs such as opiates.

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The chemotherapy clinic at Airedale Hospital, West Yorkshire, UK, has been running since before these changes were introduced—a doctor was required to sign all the prescriptions which were prepared by the pharmacist. The introduction of pharmacist prescribing simplified the pathway and allowed development of new services.

In the UK, several important national documents have highlighted the risks of chemotherapy treatment and advised services to look for innovative ways of working to ensure safer treatment for patients [1, 2]. The introduction of pharmacist-led chemotherapy clinics is one way in which some services are doing this [3-5].

In addition, the introduction of consultant oncology pharmacists means that pharmacists are well placed to take on some of the roles more traditionally associated with medical oncologists [6, 7].

This article is a brief practical guide for oncology pharmacists who are considering setting up a chemotherapy clinic.

## The groundwork

The first consideration should always be to think about whether a pharmacist-led clinic is required within the local service. There must be clear benefits for patients and for the service. It is vital that discussions take place between pharmacists, oncologists, nurses and managers. Some benefits of pharmacist-led clinics are shown in Table 1.

It is useful to include patients in discussions about new services; they can give useful insights into what they want as users of the new service. When clinical and managerial support has been established, a robust business case is required. This details the costs involved in setting up the service to include staff costs and facilities and also any income generated by the clinic. Think about what backfill may be required to cover the pharmacist's other duties and who will cover the service in the event of holiday or sickness.

If there are any similar clinics already running within the local area, arrange to visit them and speak to the staff who have already been through the process. Colleagues are usually willing to give you advice on where things went well or badly.

A very important point is to audit the current service before you make any changes. This will give you some useful information to demonstrate the benefits of your new service at a later date.

## Setting up the new clinic

It is important to identify the group of patients you will see in the clinic. In large centres this might be a specific group, such as colorectal cancer patients on capecitabine. In smaller centres it might be all capecitabine patients, or patients on oral chemotherapy treatment. Remember that you may not see many patients at first, but if the clinic is a success, the numbers will build up over time and you will need to plan ahead so that you are not over booking clinics, leading to delays for patients and stress for staff!

Consider which staff need to be involved in the clinic. Will you be running it alone or in partnership with an oncology nurse or medical oncologist, and how will patients be referred to your clinic?

Think about the facilities that will be required. There may be space in the outpatient clinic or on the chemotherapy day unit.

**Table 1: Benefits of pharmacist-led chemotherapy clinics**

| |
|---|
| **Patient benefits:**<br>• direct access to a medicines expert<br>• quicker access to medicines<br>• shorter waiting times |
| **Service benefits:**<br>• reduced costs compared with medical oncology clinics<br>• increased capacity of medical clinics<br>• reduced workload on chemotherapy day units<br>• improved team working and job satisfaction<br>• compliance with national standards |

Ensure that you have access to IT services such as blood results or prescribing systems.

It is essential that protocols are in place before you start to see patients in the clinics. This will ensure that you work within locally agreed boundaries, ensure the safety of patients and support the staff. You will need access to the patient record, which may be paper or electronic medical notes. In our chemotherapy consent clinic we have individual patient plans for each regimen and disease state. The medical oncologist signs the correct plan when the decision to start chemotherapy is made in the outpatient clinic and this acts as a referral to the pharmacy and nurse-led chemotherapy consent clinic and also as a treatment plan for prescribing chemotherapy.

Check that you have authorisation to undertake clinical tests that you might need to order. If not, then request permission from your employing hospital or put systems in place to ensure that these tests are ordered in advance. In some cases you may require test results to be available on the day of the clinic in order to prescribe chemotherapy. It may be useful to get these done the day before to ensure that the patient is not waiting.

## Running the clinic

Once the clinic details have been finalised and the clinic is ready to start, make sure that patients are clear about whom they will be seeing in the clinic. If patients are expecting to see their medical oncologist they may be concerned to see a pharmacist in the clinic. Agree the wording of clinic letters with the medical secretaries to make sure the location and timing of the clinics is clear. If you want patients to bring their medicines, or a list of medicines, then this request should be added to the clinic letter.

An important point to consider is how you will access medical assistance if needed. If you see a patient in the clinic who becomes acutely unwell or who exhibits signs of illness that require medical assessment, how will this be arranged? It may be an informal arrangement with the medical oncologist or on-call physician to call if needed, or it may be that you run your clinic alongside an oncologist so that assistance is always on hand.

Make sure that all your actions with the patient are documented in the medical record. You may need to be able to justify your actions at a later date.

## Reviewing the service

Once you have your clinic up and running, it is not time to sit back and relax! Consider the first few clinics as a pilot, following which you may wish to make changes in how the clinic runs. Think about what went smoothly and what could have been done better. Did the clinics run to time and did you have access to everything you needed?

Once the clinic is established as a long-term service then consider auditing to establish whether the proposed benefits to patients and to the service have been achieved. Compare your results with the baseline audit which you carried out before setting up the service. Consider undertaking a patient satisfaction survey.

Outcomes should be presented locally, for example at clinical governance meetings. It is important to disseminate your results more widely at meetings and conferences. Positive outcomes from your new clinic will assist other pharmacists in making the case for their new clinic.

Hopefully your new clinic will become a beacon of clinical oncology pharmacy practice. You can use it to train junior pharmacists and senior colleagues alike. Where patients have a choice about where they are treated it may also be used to attract patients to your oncology service. Finally, it may be used to attract and retain oncology pharmacists where they can use the clinic to develop their knowledge and skills in oncology working towards advanced levels of clinical practice.

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## References

1. Department of Health. Systemic anti-cancer chemotherapy, for better or worse? A report by the National Confidential Enquiry into Patient Outcome and Death. London: DH; 2008.
2. Department of Health. Chemotherapy services in England: ensuring quality and safety. A report from the National Chemotherapy Advisory Group. London: DH; 2009.
3. Booth CD, Dyminski P, Jeyasangar G. Chemotherapy Consent Clinic. Healthcare Pharmacy. Apr 2005;2(2):24-5. Available from: www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Management/References/2005 May/24/Chemotherapy-consent-clinic/
4. Donovan G, Evans S. Development of nurse/pharmacist-led clinic for the treatment of breast cancer. Adv Breast Cancer. 2005; November: 47-9.
5. Bowden EM, Horne N. 59 A joint non-medical prescribing clinic for the management of patients requiring tyrosine kinase inhibitors and chemotherapy treatments led by a lung cancer clinical nurse specialist and a Macmillan pharmacist. Lung Cancer. 71 (Suppl. 1), 2011, S20. doi:10.1016/S0169-5002(11)70059-9
6. Department of Health. Guidance for the development of consultant pharmacist posts. London: DH, 2005.
7. Kirk S. Diversity of a consultant oncology pharmacist's role. British Journal of Clinical Pharmacy. 2010;(2):23-4.

# Clinical evaluation of lenograstim use in the Bank of Cyprus Oncology Centre

The purpose of this observational study was to evaluate the effect of lenograstim (G-CSF) prophylaxis on febrile neutropenia incidence in chemotherapy-receiving patients with solid tumours.

## Introduction

### Febrile neutropenia

Cytotoxic chemotherapy suppresses the haematopoietic system impairing host-protective mechanisms. Neutropenia, the most serious haematologic toxicity, can lead to febrile neutropenia (FN), which usually requires immediate hospitalisation and antibiotic treatment [1, 2]. The mean level of in-hospital mortality associated with patients hospitalised with FN is 9.5%. This percentage rises above 21% for patients with co-morbidities [3]. Chemotherapy dose reductions and dose delays, as a result of neutropenia and FN, can lead to reduced patient survival [4, 5].

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### The granulocyte-colony stimulating factors

Granulocyte colony-stimulating factors (G-CSFs) stimulate the proliferation and survival of neutrophils and their precursors, thereby reducing the incidence and severity of neutropenic complications across a range of malignancies, and facilitating the delivery of full-dose chemotherapy [6]. Lenograstim is the glycosylated recombinant form of human G-CSF. Several randomised controlled trials have confirmed the efficacy and safety of these agents, and a meta-analysis involving chemotherapy-receiving adult cancer patients was recently performed [7]. All forms of G-CSF evoked significant reductions in FN risk in both solid tumour patients and those with non-Hodgkin's lymphoma. Notably, a significant reduction in FN risk was observed across a broad range of baseline levels of risk ranging from 17 to 90%. A significant reduction in infection-related and early all-cause mortality was also demonstrated. These observations are consistent with that of a Cochrane meta-analysis of therapeutic CSF in patients hospitalised with FN following cancer chemotherapy [8]. The meta-analysis also confirmed the ability of these agents to sustain chemotherapy-relative dose intensity.

### Economic considerations

Despite the ability of G-CSFs to reduce the risk of serious chemotherapy-related toxicities, many patients who receive myelosuppressive chemotherapy do not receive concomitant myeloid growth factors. While the decision to utilise a G-CSF in chemotherapy patients should be based primarily on clinical indications, the cost of these agents often raises economic considerations at the institutional and societal level. The direct costs of myeloid growth factors should be balanced against the reduction in costs of FN hospitalisation, the reduction in early infection-related mortality, and overall survival. It is anticipated that by identifying patients who are most at risk from these complications, i.e. those who are most likely to benefit from prophylactic myeloid growth factors, the risk of these serious complications could be reduced in an efficient and cost-effective manner.

### Clinical practice guidelines

Clinical practice guidelines for the use of G-CSFs have been developed by various professional organisations, including the European Organisation for Research and Treatment of Cancer (EORTC) [9], the National Comprehensive Cancer Network [10], and the American Society of Clinical Oncology [11]. They agree that any patient with an FN risk greater than 20% should receive primary prophylaxis with G-CSF alongside each chemotherapy cycle. In some instances, the chemotherapy regimen itself carries an FN risk that exceeds this threshold. If the FN risk associated with the regimen is 10–20%, the physician should consider whether patient factors take the overall risk beyond 20%. If the chemotherapy regimen is considered to present an FN risk of less than 10%, primary prophylaxis with G-CSF should not be offered, unless the risk of serious FN complications is considered high.

## Patients and methods

An evaluation of the use of lenograstim in actual practice as measured by the incidence of subsequent FN in patients with solid tumours who undergo chemotherapy would be useful for clinicians who are seeking to develop an evidence-based reimbursement policy for these drugs.

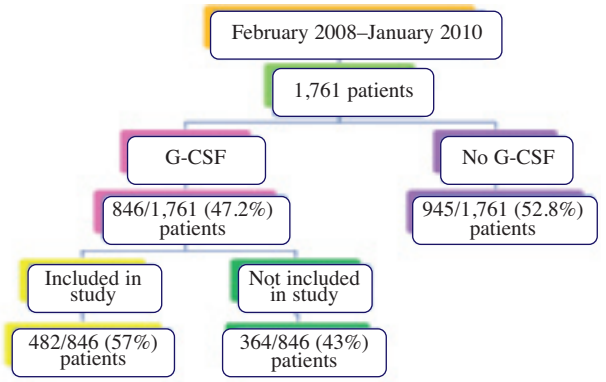
Consequently, we conducted such a study in the Bank of Cyprus Oncology Centre, Nicosia, Cyprus. A total of 482 patients who received G-CSF between February 2008 and January 2010 were identified and selected from the pharmacy computer system Power Pro. Patient data and blood test results were retrospectively obtained from medical records and Mosaiq software, a standard data collection form was developed, and the following information was recorded: height, weight, date of birth, diagnosis, stage of disease, and details of prior or concomitant radiotherapy. Any delays in the administration of chemotherapy (with explanations) were recorded, as was the absolute neutrophil count at the time of delay, and details of whether the patient had experienced neutropenia during the cycle in question. When the dose of administered chemotherapy was less than optimal, the reason for the dose reduction and the relative percentage of the administered dose versus the

planned dose were recorded. Use of G-CSF and antibiotics—reason, dose and frequency of administration, total number of doses—were also recorded. Results were recorded in Microsoft Excel and analysed using an SPSS database.

## Results

Between February 2008 and January 2010, 1,791 patients admitted to the Centre received chemotherapy. Eight hundred and forty-six (47.2%) patients received lenograstim after myelosuppressive chemotherapy. Of these 846 lenograstim courses, 482 (57%) were included in the study, see Figure 1.

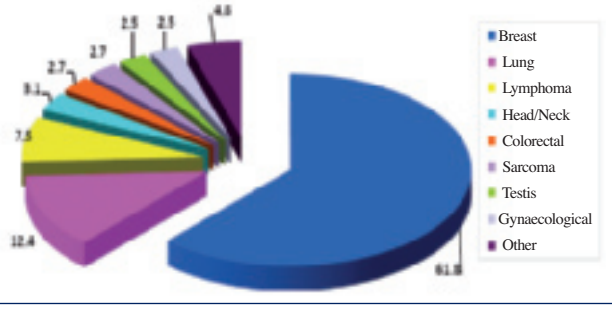
**Figure 1: Patients receiving lenograstim between February 2008–January 2010**




### Lenograstim administration

A total of 12,037 administrations of lenograstim were recorded in 482 patients. The median number of injections administered per patient per chemotherapy cycle was 5 (range 1–10 injections). In most patients, administration was initiated either 48 hours (57% of cases) or 72 hours (36% of cases) post-chemotherapy. Overall, 76.1% (367/482) of patients received prophylactic administration of lenograstim. The distribution of cancer types was 61.8% (298/482) breast, 12.4% (60/482) lung, 7.5% (36/482) lymphoma, 3.1% (15/482) head/neck, 2.7% (13/482) colorectal, 2.7% (13/482) sarcoma, 2.5% (12/482) testicular, 2.5% (12/482) gynaecological, and 4.8% (23/482) other, see Figure 2. The majority of recruited patients were female (75%), consistent with this tumour-type distribution.

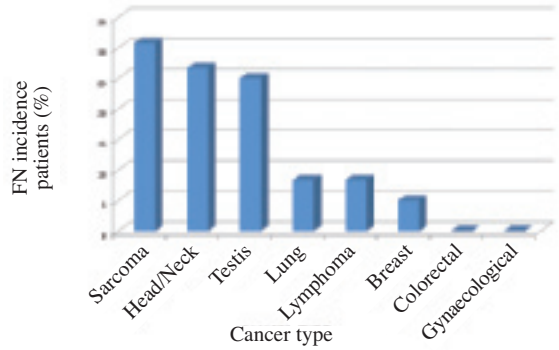
**Figure 2: Patient diagnosis**




### Incidence of FN

Following primary prophylaxis with lenograstim, the incidence of FN varied between the different cancer types. The malignancies associated with the highest FN incidence were sarcoma and head/neck cancer [30.8% (4/13) and 26.7% (4/15), respectively]. Breast cancer was associated with the smallest FN incidence [5% (15/298)], see Figure 3.

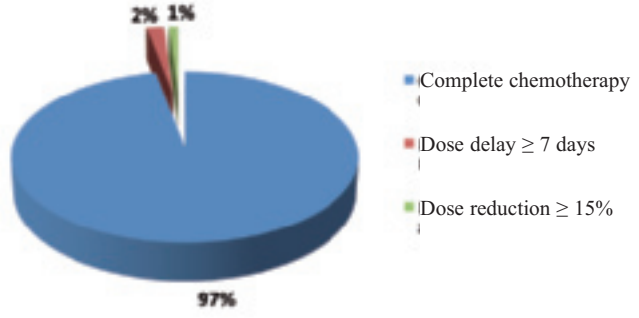
**Figure 3: Incidence of FN after lenograstim administration**




### Delivery of full-dose chemotherapy

Ninety-seven per cent (468/482) of patients received full-dose chemotherapy as per protocol. Overall, nine courses of chemotherapy were delayed for ≥ 7 days in 9/482 (2%) patients, and 5/482 (1%) patients required dose reduction ≥ 15% due to prolonged neutropenia, see Figure 4.

**Figure 4: Delivery of full dose chemotherapy**




### Antibiotic therapy

Ninety-six episodes of FN (82 patients) requiring hospitalisation occurred while patients were receiving prophylactic G-CSF. The mean duration of hospital stay was five days. Sarcoma and lung cancer patients required the longest period of hospitalisation (mean six days). The empiric antibiotic of choice was piperacillin/tazombactam + gentamycin, as administered in 82.4% (79/96) patients. Ciprofloxacin 500 mg was administered in 73.6% (50/68) patients. Positive cultures were found only in seven patients (8.5%). Of the organisms isolated, 5/7 (71.4%) were gram-positive bacteria and 2/7 (28.6%) were gram-negative bacteria.

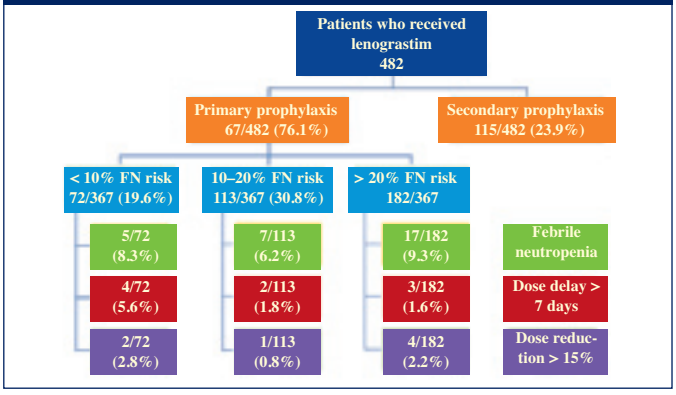
### Adverse events

Various adverse events were observed following primary prophylaxis with G-CSF. The most frequently reported adverse event was bone pain, which was recorded in 30.7% (148/482) of patients. This bone pain was mild to moderate in severity, and in most patients (83.8%), was successfully treated with paracetamol.

**Assessment of risk for neutropenic complications according to EORTC guidelines**

According to EORTC guidelines for G-CSF administration, 19.6% (72/367) of our patients who received primary prophylaxis would be categorised in the low-risk FN category, 30.8% (113/367) would be categorised in the intermediate-risk category, and 49.6% (182/367) would be categorised in the high-risk category. Our low-risk patients reported a smaller incidence of FN, but a higher incidence of neutropenic complications, suggesting that prophylactic administration of growth factors in these patients improved overall outcome. Numbers, however, were small, see Figure 5.

**Figure 5: Assessment of risk for neutropenic complications as per EORTC guidelines**




## Conclusion

The results of our study showed that almost half of the patients who received chemotherapy in the Centre also received lenograstim. More than half of these patients were women with breast cancer. Following lenograstim primary prophylaxis, almost all patients received full-dose chemotherapy without any modifications.

Our results also showed that G-CSF may currently be misdirected toward low-risk patients, incurring unnecessary expense. According to guidelines, G-CSF treatment has limited cost-effectiveness in low-risk patients, in whom alternative management approaches are safe and inexpensive. Conversely, in extremely high-risk populations, it is unlikely that G-CSF therapy could decrease costs, since early hospital discharge is rarely feasible. Therefore, it is probably an intermediate-to-high-risk population that is most likely to benefit from G-CSF therapy, and thus, lenograstim should be used as part of the standard therapy in the management of FN patients with solid tumours meeting these risk criteria.

It is evident that healthcare practitioners should improve G-CSF use in the hospital setting to facilitate cost-effective therapy. Our results have assessed many factors, which may lead to modifications in practice, new guideline recommendations and better outcomes in the Centre. Perhaps every cancer hospital should undertake their own assessment and produce their own guidelines for managing such patients. Further studies are warranted to determine the best efficacious and cost-effective G-CSF prophylactic options for patients at each level of risk.

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## References

1. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004;100(2):228-37.
2. Dale DC, McCarter GC, Crawford J, Lyman GH. Myelotoxicity and dose intensity of chemotherapy: reporting practices from randomized clinical trials. J Natl Compr Canc Netw. 2003;1(3):440-54.
3. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006;106(10):2258-66.
4. Bosly A, Bron D, Van Hoof A, De Bock R, Berneman Z, Ferrant A, et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann. Hematol. 2008;87(4):277-83.
5. Chirivella I, Bermejo B, Insa A, Perez-Fidalgo A, Magro A, et al. Impact of chemotherapy dose-related factors on survival in breast cancer patients treated with adjuvant anthracycline-based chemotherapy. J Clin Oncol. 2006;24(18S):668.
6. Lyman GH, Kuderer NM, Djulbegonic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. Am J Med. 2002;112(5):406-11.
7. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol. 2007. 20;25(21):3158-67.
8. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol. 2005;23(18):4198-214.
9. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumors. Eur J Cancer. 2006;42(15):2433-53.
10. Crawford J, Althaus B, Armitage J, Balducci L, Bennett C, Blayney DW, Cataland SR, et al. National Comprehensive Cancer Network (NCCN). Myeloid growth factors. Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2007 Feb;5(2):117.

## ANNOUNCEMENT

European Journal of Oncology Pharmacy (EJOP) is the first publication in oncology pharmacy in the world, and is recognised as the leading publication in oncology pharmacy in Europe.

Starting from 2007, Volume 1, Issue 1, EJOP has been indexed in the Directory of Open Access Journals (DOAJ).

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## Cold water reconstitution of Vidaza® with subsequent refrigerated storage prolongs drug stability

### References (please see article on pages 24–25)


1. Giralt SA, Horowitz M, Weisdorf D, Cutler C. Review of stem-cell transplantation for myelodysplastic syndromes in older patients in the context of the decision memo for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome emanating from the centers for medicare and medicaid services. J Clin Oncol. 2011;29(5):566-72.
2. Beisler JA. Isolation, characterization, and properties of a labile hydrolysis product of the antitumor nucleoside, 5-azacytidine. J Med Chem. 1978; 21(2):204-8.
3. Daher GC, Harris BE, Diasio RB. Metabolism of pyrimidine analogues and their nucleosides. Pharmacol Ther. 1990;48(2): 189-222.
4. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10:223-32.
5. ICH Guidance Q2 (R1). Validation of analytical procedures: text and methodology. November 2005. Available from: http://www.ich.org/fileadmin/ Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1_Guideline.pdf
6. ICH Guidance Q6 A. Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances. October 1999. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_ Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf
7. ICH Guidance Q1 A (R2). Stability testing of new drug substances and products. February 2003. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf

# Hospital workers perceptions about nano-technology

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Nanotechnology is the tiny world of controlling matter at the scale of one billionth of an atom. In the last few years, nanotechnology has catapulted from being the specialty of a few physicists and chemists to a worldwide scientific and industrial enterprise.

## Introduction

The rapid development of nanotechnology and the growing importance of this technology for everyday life have not really attracted any attention from the public at large. However, little is known about the technology's possible health and environmental implications. At this critical juncture, it is important that leaders from industry, government, the science and engineering community, and other sectors develop a better understanding of what the public wants and expects of these new and emerging technologies [1-3].

The number of projects that encourage the public to engage with nanotechnology is growing all the time. However, some scientists are uncomfortable with the idea that non-experts should have active roles in decisions about nanotechnology, because they are often uninformed. Regardless of this opinion, public engagement is becoming a serious component of nanotechnology policy in many countries [1-6]. Public perception will have a major influence on the success of new applications of nanotechnology, as will the results of risk assessments carried out by industry on the various nanotechnology applications [1, 5-8].

## Objective

The aim of this study was to evaluate hospital employee perception about nanotechnology in Saudi Arabia and correlate it with existing demographic data.

## Methodology

Three hundred surveys were distributed to employees and trainees from different departments in our hospital. The response rate to the survey was 40% (120/300). Thirty-nine surveys (33%) were excluded because less than 70% of the questionnaire was completed. The survey included nine core questions which measured hospital workers awareness, perceptions and preferences of nanotechnology. Demographic measures, such as age, sex, profession, years of experience and level of education, were also recorded.

## Results

### Demographics

Table 1 shows that we managed to achieve a relatively representative distribution of men and women in our sample, with 51% of respondents being female. The highest percentage of participants (29%) were aged between 30–40 years and the lowest percentage (9%) were aged between 50–60 years. At least 68% of respondents had achieved a bachelor's degree and 21% had a doctorate or equivalent level. A slight majority of respondents (52%) were pharmacists, whilst 21% were physicians. Thirty-five per cent of respondents had less than five years' experience.

By correlating age with whether workers had heard about nanotechnology, we observed a similarity between the group aged between 18–25 years and the group aged between 30–40 years. Sixteen per cent of each of these two groups reported that they had heard of nanotechnology, whilst 11% did not. Six per cent of the groups aged 25–30 years and 40–50 years stated that they had not heard of nanotechnology, whilst 10% and 14% respectively, had. In the 50–60 years age group, 5% had and 5% had not.

With regards to education, the highest percentage of employees who had heard of nanotechnology were those with a doctorate or equivalent degree. This was followed by university graduates, university undergraduates, and those with a Masters degree (19%, 15%, 12%, and 9% respectively).

**Table 1: Demographic data (N = 81)**

| **Age** | **18–25** | **25–30** | **30–40** | **40–50** | **50–60** |
|---|---|---|---|---|---|
| | 21 (26%) | 13 (16%) | 23 (29%) | 16 (20%) | 7 (9%) |
| **Sex** | **Male** | **Female** | **N/A** | | |
| | 34 (42%) | 41 (51%) | 6 | | |
| **Level of education** | **Doctorate** | **Master** | **University graduate** | **University undergraduate** | **Diploma or high school** |
| | 17 (21%) | 10 (13%) | 27 (34%) | 16 (19%) | 11 (13%) |
| **Profession** | **Medicine** | **Pharmacy** | **Nursing** | **Others** | |
| | 17 (21%) | 42 (52%) | 12 (15%) | 10 (12%) | |
| **Years of experience** | < 5 | 5–10 | 10–15 | 15–20 | > 20 |
| | 28 (35%) | 16 (20%) | 14 (17%) | 7 (8%) | 10 (12%) |

N: total number of participants; N/A: not applicable.

**Table 2: Questions and answers**

| | | | | | |
|---|---|---|---|---|---|
| Have you heard about nanotechnology? | **Yes** 50 (61%) | | **No** 31 (39%) | | |
| How much have you heard, read or seen about using nanotechnology? | **A lot** 5 (7%) | **Some** 18 (22%) | **A little** 32 (40%) | **Nothing** 11 (14%) | **Not sure** 3 (4%) |
| How did you know about nanotechnology? | **Conference** 20 (25%) | **Media** 32 (40%) | **Internet** 21 (26%) | **Books** 5 (6%) | **Others** 6 (7%) |
| I support use of nanotechnology for human enhancement | **Agree** 41 (51%) | **Slightly agree** 9 (11%) | **Do not know** 16 (20%) | **Slightly disagree** Not applicable | **Disagree** 1 (2%) |
| What is your initial impression of risks and benefits of nanotechnology? | **Benefits** outweigh risks 31 (38%) | **Benefits and risks** are equal 12 (15%) | **Risks outweigh** benefits Not applicable | **Not sure** 22 (27%) | |
| Rate the impression of nanotechnology to science and business in the next five years | **Very important** 38 (47%) | **Fairly important** 17 (21%) | **Not too important** Not applicable | **Not at all important** Not applicable | **Do not know** 12 (15%) |
| Do you feel that you need to know more information about nanotechnology? | **Yes** 61 (75%) | **No** Not applicable | **Not interested** 5 (6%) | | |
| Do you recommend to policy makers to provide more information to hospital workers about nanotechnology? | **Yes** 49 (61%) | **No** Not applicable | **Do not know** 16 (20%) | | |

In terms of experience, the highest percentage of employees that had heard of nanotechnology was those with less than five years of experience. This was followed by those with 10–15 years, those with 5–10 years, those with over 20 years, and those with 15–20 years (17%, 12%, 11%, 7%, and 5% respectively).

**Survey question answers**

Table 2 shows that in general, 61% of people in Saudi Arabia reported that they had heard of nanotechnology. The largest proportion of respondents (40%) indicated that they heard a little about nanotechnology. The majority of the respondents (40%) had heard about nanotechnology through the media, while the remaining proportion knew about nanotechnology from conferences, Internet, books, and other sources respectively. A slim majority of respondents (51%) agreed with the statement, 'Overall, I support the use of nanotechnology for human enhancement'. Thirty-eight per cent agreed that the benefits of nanotechnology outweighed its risks, 15% agreed that its benefits and risks were equal, and 27 % were not sure about the risk and benefits of nanotechnology. The majority (47%) indicated that they considered that nanotechnology would be very important to science and business in the next five years, 21% considered that it would be fairly important, and 15% were unsure. Almost 75% indicated that they required more information about nanotechnology.

The majority of respondents also tended to associate nanotechnology usage equally within medicine and pharmacy (67% and 65% of respondents respectively).

## Conclusion

Anticipatory governance of emergent technologies depends on a comprehensive understanding of the values in society that shape public understanding and opinion of new and emerging technologies, and of related current technologies. This survey aimed to measure and evaluate the understanding of public values about nanotechnology in Saudi Arabia, as presented by hospital workers. Public opinion research should be considered a vital element in any attempt to assess a developing technology, and in any subsequent efforts at anticipatory governance. Further research is highly recommended. In addition, we recommend that policy makers should increase hospital employee awareness about nanotechnology through continuous scientific events. This may lead to improved understanding and indirect future advances in nanotechnology. We plan to re-evaluate and assess the workers' perceptions in five years time. A comparison of available data with the international public perception about nanotechnology is also recommended.


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## References

References can be found on page 17.