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27–29 September 2012, Budapest, Hungary

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

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ISSN EJOP: 1783-3914

Print Run: 3,000 Printed by PPS sa



Published in Belgium  
by Pharma Publishing &  
Media Europe  
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### 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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# Willingness to communicate in health care – a multi-professional approach

Over the past few years, many articles and research reports have focused on the willingness to communicate. This choice of words refers to the idea that language learners who are willing to communicate in a second language actively seek opportunities to communicate finally in both languages.

Pharmacists sometimes feel that they are out of date in their command of relevant vocabulary, particularly when talking to physicians about the topic of therapeutic treatment. Recognising this situation, the European CanCER Organisation, has changed its constitution and implemented the word 'multi-professional' to go alongside the well-known term 'interdisciplinary'.

Different European countries have different perspectives on the role of pharmacists, owing to the various influences of history and economics. When it comes to oncology, however, there is a particular need for comprehensive care in which pharmacists have a pivotal role.

This year, ECCO will host an Oncopolicy Forum with the title 'The Future of Personalised Cancer Medicine in Europe'. This will launch a multidisciplinary debate on the challenges ahead and the joint roles and responsibilities of key stakeholders in forging a European policy environment that supports advances in the field.

The goal of the Oncopolicy Forum is to ensure mobilisation of the oncocommunity towards continued cooperation in responding to the needs of European citizens. The annual Forum is an innovative platform for inspiring cancer policy debate at EU level. It brings together a multi-stakeholder audience spanning the entire oncology spectrum to debate openly and share experiences and tools in an effort to reach a common insight for fighting cancer in partnership.

As pharmacists, we have to recognise the need to learn our second language well. This requires understanding the need to exchange with physicians and nurses in order to work towards our common goal.

Pharmacists are not only talking to themselves: this issue of EJOP includes the topics 'Extended stability of rituximab, bortezomib and azacitidine for use in haematology', as well as 'The use of bar codes in hospitals – a pharmaceutical perspective'.



Klaus Meier  
Editor-in-Chief

EJOP

Besides these articles, we are initiating a discussion on treatment outcomes with 'Therapeutic drug monitoring in clinical oncology', together with highly informative pieces on 'Biosimilars in oncology: emerging and future benefits'; 'Cardiotoxicity induced by anticancer drugs'; and 'New treatment options for bone metastases in metastatic prostate cancer'.

Not only healthcare teams but also politicians participate in the debate on the 'Rising cost of cancer care and chemotherapy drug shortages'.

In July 2012, European Commissioner for Health and Consumer Policy, Mr John Dalli called on our Society (ESOP) to follow the work of EMA and its scientific committees. The committees include representatives of patient organisations and healthcare professionals. The Commission aims to ensure that EU patients benefit from strict medicine controls. It is therefore crucial to the success of this work that the committees take into account the needs of both patients and healthcare professionals.

Members of the European Society of Oncology will join the Committee of Advanced Therapies and the Pharmacovigilance Risk Assessment Committee to ensure that they meet the interests of cancer patients—both those undergoing therapy and those receiving chronic treatment.

Related with PGEU (Pharmaceutical Group of European Union) which is representing all European community pharmacists, and in close partnership with EAHP, the European hospital pharmacists association; our society, ESOP, is acting as the voice in oncology pharmacy for all European pharmacists.

The increasing use of oral cytotoxic agents makes the mission clear: the interactions between these drugs and food as well as with normal medications, and the management of side effects, is placing higher-than-ever demands on pharmacists.

At the first European Conference of Oncology Pharmacy (ECOP) on 27–29 September 2012 in Budapest, Hungary, we shall demonstrate the strengths of our members as well as our partnerships with ESMO (European Society for Medical Oncology) and patient organisations.

We are making excellent progress in learning our second language in order to advance collectively innovations in cancer treatment in Europe, for the benefit of patients.

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# Practical stability studies: a powerful approach for reducing the cost of monoclonal antibodies

Contrary to manufacturer's product specifications, the stability over time of monoclonal antibody-based drugs is greater than widely assumed, according to extensive investigations on the effects of different conditions on physicochemical and *in vitro* properties.

**M**onoclonal antibodies (mAbs) are considered to be a 'therapeutic revolution': a new generation of blockbuster drugs that has replaced traditional drugs such as proton pump inhibitors, hypolipodemic agents or antipsychotic drugs [1]. Over the past two decades, mAbs and fusion proteins have provided a breakthrough in the treatment of seriously disabling diseases or otherwise fatal conditions. Therapeutic proteins are also a highly prized treatment for rare diseases, usually severe, for which previous approaches were inefficient. In many cases, however, their use is a last resort for patients. Given the high cost of development, the benefit in terms of cost-efficiency is very limited indeed. Two disease areas are particularly involved: autoimmune diseases and oncology. With regard to the former, mAbs are prescribed by gastroenterologists for Crohn's and ulcerative colitis, and by rheumatologists and dermatologists for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. The most frequently prescribed products are anti-TNF and the related infliximab, etanercept, and adalimumab. The latter is expected to be the leading pharmaceutical by 2016, exceeding US\$10 billion a year in sales.

Monoclonal antibodies used in oncology are also likely to reach billions in sales. Bevacizumab, expected to become the second highest product in sales by 2016, is indicated in several types of cancer cells. Rituximab, trastuzumab and cetuximab will also be among the top ten of drug sales. Whereas there were no biotech products among the world's 10 best-selling drugs in 2000, they are expected to comprise eight of the top ten in 2016, with mAbs monopolizing seven of these. In addition to these gems, other 'emerging' antibodies have major financial potential such as ranibizumab, omalizumab, palivizumab, and enosumab; a myriad of new mAbs are also in the pipeline, these products are mainly prescribed by hospital specialists. Although not commonly available in community pharmacies, the financial impact of their use is enormous and is only poorly controlled by third parties such as insurance companies and national social security systems. In Europe, sales of mAbs are growing at 12–15% per year compared to a near zero growth rate for the European economy. The key question, therefore, is how to pay for these new drugs? Besides pharmacoeconomic approaches based on the cost-efficiency ratio for each drug and disease, including modification of prescription guidelines or careful patient-by-patient analysis for each prescription by oncology pharmacists,



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complementary approaches such as practice optimization may also control costs, including post-licensing studies on the stability of mAbs.

Stability studies performed by the pharmaceutical industry are designed only to fulfil licensing requirements [2, 3], with little attention to how these drugs are to be used in clinical practice. Instructions contained in package inserts assume that a drug will be dissolved and administered immediately on a clinical ward. Increasingly, however, the situation for hospital medications may be different. As clinical practice may deviate

from licensing requirements we notice a gap between data contained in package inserts, or the SmPC, and practical needs. For example, post-dilution or post-reconstitution stability data are frequently limited to 24 hours solely to prevent bacterial growth, whereas chemical stability could be much longer. In practice, pharmacy-based centralized preparation may have to take place days in advance, with the filling of ambulatory devices for continuous infusions or batch preparations for dose banding. To assume limited stability for expensive products without justification is obviously very costly. Thus, there is a strong need for additional stability data for anticancer drugs. Recently, European guidelines on the stability of anticancer drugs were published under the auspices of the French Society of Oncology Pharmacy, which represents France at ESOP [3, 4]. These include a specific chapter on therapeutic proteins. A review paper on this topic has also been published recently [5].

The main problem is the difficulty of assessing the stability of new biotechnology products such as mAbs [6]. These sensitive products can degrade through a more complex set of pathways than classical drugs due to the various manipulation steps involved in their preparation. The *in vivo* activity of proteins depends not only on their primary structure (sequence) but also on their structure in 3-dimensional space (secondary, tertiary and quaternary structures). Their protein conformation could change subtly when exposed to mild chemical or physical stresses such as shaking, small temperature change, variations in ionic strength, light, exposure to oxygen or to traces of metals [3, 4].

Monoclonal antibodies (mAbs) have good stability compared to other proteins. Indeed, immunoglobulins are normal constituents of the blood and their natural half-lives are about 3 weeks in what may otherwise be thought of as unfavourable conditions (37°C in the presence of degrading enzymes). In support



of this, the half-life of bevacizumab *in vivo* is also 3 weeks. It is therefore reasonable to assume that an unopened vial of bevacizumab, accidentally stored for 1–2 days at room temperature, will not be significantly altered. However, according to the manufacturer's recommendations, stocks should be discarded if the cold chain becomes interrupted, in the case of refrigeration failure over a weekend, this is a very expensive waste! Thus, regardless of the financial interests of pharmaceutical companies and to provide hospital pharmacists with a scientific basis for avoiding this costly practice, our team has, over several years, developed a research theme on the stability of mAbs. Initially, we studied the thermal stability of diluted bevacizumab and cetuximab and found no alteration even after 3 months at 37°C [7]. These results encouraged us to investigate further this exciting and largely unexplored area.

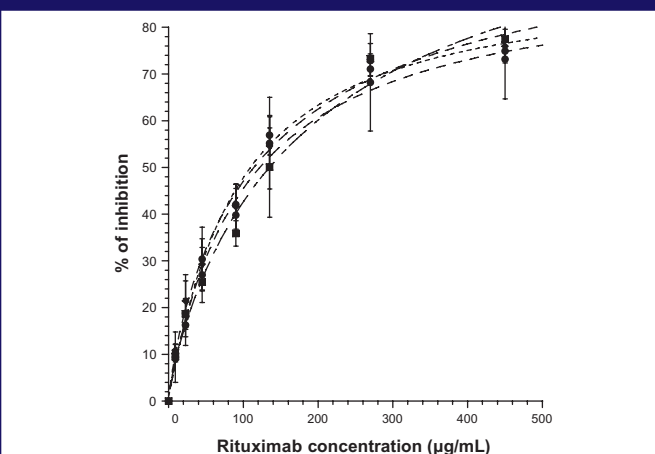
Protein instability implies two main types of alteration with several possible pathways: (i) physical instability: aggregation, denaturation or adsorption on surfaces; (ii) chemical instability: desamidation, disulfide bond breakage, hydrolysis, isomerisation, non-disulfide crosslinking, or deglycosylation. The main causes of instability include temperature (elevation or freezing), formulation pH, adsorption, salt effects, oxidation (associated with metal ions and chelating agents), shaking or shearing and concentration. Many of these conditions can be found during the handling process in the pharmacy or on the ward. Unexpected instability can be induced very subtly by simple processes such as stirring or filtration due to substances that can leach from the surfaces of filters or syringes [6, 8]. Stability assays for therapeutic proteins must therefore involve several specific studies and represent a considerable analytical challenge.

For a complete stability profile, several complementary (orthogonal) methods are necessary including at least three complementary separating methods [3]. A good stability study also requires stressed conditions to ascertain the relevance of the chosen analytical methods. For tests on proteins, these should include not only high temperature stress but also low temperature conditions such as freezing. This can trigger instability not through chemical alteration but by physical processes such as aggregation, which is unlikely with classical low molecular weight drugs. Mechanical stress can also induce aggregation. For example, we have found a new commercial formulation of the drug cetuximab to be less sensitive than the old formulation to the effect of mechanical stress (stirring) owing to the presence of a tensioactive agent [10]. We have also studied the influence of pneumatic conveying systems on the stability of diluted rituximab in polyolefin bags. With as many as eight circulations through the system, and without introducing air, there was no modification in comparison with a control (no circulation). However, in presence of air, we found clear modifications after four routes. We concluded that, in practice, the pneumatic system can be used for the transport of proteins but the introduction of air into the bags promotes instability [11]. These results imply that, in the case of delayed or cancelled administration, a rituximab bag can be safely returned to the pharmacy and returned to

the ward by the same conveyancing system. These results are critically important since up until now, many pharmacists have been instructed by their respective inspection bodies to discard unutilized bags, with obvious cost consequences.

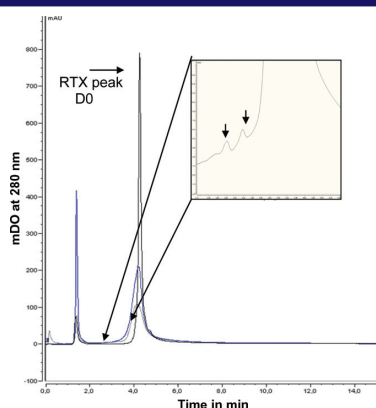
As our clinicians accept the use of dose-banding for some mAbs such as rituximab, we currently prepare batches of this mAb in advance (700 mg and 600 mg per 500 mL bag) under GMP conditions (ISO 5) that give assurance of bacteriological quality and permit full analytical control of each batch. This practice is based on our long-term stability study demonstrating that bags kept at 5°C ± 3°C were chemically and physically stable for more than 6 months [12]. Various protein characterization methods were used to assess possible changes in physicochemical properties, including size-exclusion and cation-exchange chromatography, dynamic light scattering, turbidimetry, thermal denaturation curves, second-derivative ultraviolet and infrared spectroscopy, and peptide mapping. We have also demonstrated that the biological activity of rituximab was fully conserved (toxicity on anti-CD20 expressing cells). A complementary study under stressed conditions (storage at 40°C) showed that all methods employed were appropriate for indicating stability. Typical results are presented in Figures 1 and 2. The savings per year due to dose-banding may appear modest, but they are significant, considering the total purchase cost of purchasing rituximab: we saved about 2%, or Euros 50,000 from a total of Euros 3,000,000 and about 150 work hours of technicians. We should also consider improvements in the quality and safety of prepared bags, better workload organization and reduced treatment delays for patients, all benefits that are difficult to quantify in financial terms.

**Figure 1: Rituximab (RTX) direct cytotoxicity on CD20-expressing cells\***



\*Cytotoxicity was not different after 6 months at 4°C. Rituximab (RTX) direct cytotoxic on CD20-expressing cells was determined through concentration-dependent cytotoxicity curves (concentration of RTX: 0, 4.5, 9, 22.5, 45, 90, 135, 270 and 450 µg/mL) on a human lymphoma cell line (RAJI lymphoma cells (ATCC number: CCL-86)). Twelve wells were seeded for each concentration tested. The results were expressed as the percentage of inhibition in comparison to control (without RTX). The cytotoxic effects of RTX were the same after six months of storage at 4°C (adapted from reference 11).

**Figure 2: Cation-exchange chromatographic profile of rituximab (1 mg/mL)**



Cation-exchange chromatographic profile of rituximab (1 mg/mL) using a WCX-10 column at pH 6.0 eluted with a linear salt gradient from 0 to 50% of 1M NaCl and detection at 280 nm. Decrease in AUC was observed at 40°C from three months and reaching 45% at six months. Changes of shape of main peak were also observed. Two new peaks were found just before the main peak after six months at 40°C (inset). No change was seen after 6 months at 4°C (adapted from reference 11).

A recent German study showed that reconstituted trastuzumab was stable for up to 1 month [13]. However, this result confirmed the manufacturer's stability data only with regard to reconstitution with bacteriostatic water, while the same product reconstituted with water for injection is said only to be stable for 48 hours [14]. Even if expected, these results clearly demonstrate that the manufacturer's proposed stability limit was based on the risk of biological contamination rather than physicochemical stability, as found previously [2-4]. However, to investigate the potential for dose-banding with trastuzumab, we performed a detailed long-term stability study demonstrating that diluted trastuzumab (0.8 and 2.4 mg/mL in saline in polyolefin bag) is strongly physicochemically stable up to 6 months at 4°C [15]. This extended stability could enable advance or batch preparation by pharmacy centralized units. Such long-term stability data are required for the development of a dose-banding approach to mAbs, underscoring the importance of further high quality research in this field.

## Conclusion

In conclusion, our results demonstrate that the time frame for the use of mAbs in oncology can be extended safely, allowing, for example, early reconstitution, workload optimization or safe storage of a patient's bags for several days. Our results also support the possibility of preparing standardized batches of 'ready-to-use' diluted mAbs according to good manufacturing procedures that ensure sterility and quality control. We have demonstrated that extending the anticipated stability time limit of mAbs can help pharmacists to maximize cost-efficiency even if the benefit appears modest. The more that a dose-banding approach is taken with mAbs, the more financial benefits can be gained. Even just retaining unused bags, or the use of already opened vials for several patients, will have a significant impact.

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# Therapeutic drug monitoring in clinical oncology: pros and cons

Therapeutic drug monitoring (TDM) has the potential to be highly effective in optimizing the outcome of cancer treatments, yet it is under-used. This article explores many reasons for and against the use of TDM to minimise the risk of complications and side effects during oncology therapy and argues in favour of adopting the approach more widely.

## Introduction

Therapeutic Drug Monitoring (TDM) has been well established in several areas of pharmacotherapy, for example, during the use of special anti-infectives (aminoglycosides, vancomycin), anticonvulsive drugs (phenytoin, carbamazepine) or psychoactive agents (lithium).

The main purpose of TDM is to maintain patients in a defined therapeutic window in order to avoid: (1) subtherapeutic drug levels provoking disease-related complications, and (2) supratherapeutic plasma concentrations associated with an increased risk for severe drug-related side effects. This will need to be intensified if plasma concentrations are likely to vary extensively between individuals over a short time period.

Regular TDM has the potential to be highly useful in cancer chemotherapy as most cytotoxic drugs have a very narrow therapeutic index as well as considerable fluctuations in drug plasma levels following oral or IV medications based on patients' body surface area. Besides methotrexate (MTX), however, TDM is not yet routinely established for anticancer therapy [1].

## TDM of anticancer drugs – pros

Over the past few decades several cases have demonstrated the potential advantages of TDM in clinical oncology: Gamelin et al. were among the first to suggest that TDM may improve clinical effectiveness in relation to survival following systemic administration of the antimetabolite 5FU. A considerable increase in the time to disease progression was achieved in patients with metastatic colorectal cancer who were kept in a predefined therapeutic range during continuous infusion, e.g. 2–3  $\mu\text{g/mL}$ , of 5FU, compared to patients treated without TDM [2]. These preliminary experiences have been confirmed recently. In addition, even with 5FU as adjuvant therapy, TDM could improve clinical outcome. Fluctuations of 5FU plasma levels are clearly correlated with the underlying expression of the corresponding catabolic enzyme dihydropyrimidine dehydrogenase [3].

Intensified MTX-containing regimens are associated with an increased risk for severe nephrotoxicity. TDM is therefore mandatory, for example, 42 hours after starting of drug infusion in order to assess individual drug elimination kinetics, see Table 1.



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If the antifolate critically persists over time, one has to: (1) exclude any interacting co-medication, for example, Piperacillin, NSAID; or other surrounding worsening conditions, for example, diarrhoea; as well as (2) intensify Leucovorin rescue, hydration and alkalization on demand. Besides toxicity prevention, TDM may be a beneficial marker for the prognosis of osteosarcoma treatment [4, 5].

In the case of carboplatin, Jodrell et al. were able to define a therapeutic window with an AUC ranging from at least 4  $\text{mg/mL} \times \text{min}$  to 7.5  $\text{mg/mL} \times \text{min}$  (at maximum) in patients with advanced ovarian cancer. Values beneath may provoke disease progression, whereas values beyond are associated with severe thrombocytopenia without any perspective for improved tumour control. The challenge to hold patients within the defined therapeutic window has been clearly overcome by introducing the Calvert-formula, which enables an individualized and pharmacokinetically guided carboplatin cancer chemotherapy based on renal function [6].

TDM is also of potential benefit in certain other situations. Przepiora et al. were among the first to present preliminary data on the potential role of TDM in patients undergoing peripheral blood stem cell transplant. They suggested that considerable cytotoxic drug levels, e.g. TEPA, may persist in individuals following high-dose chemotherapy, which might severely affect the success of engraftment following reinfusion of stem cells [7].

**Table 1: Therapeutic drug monitoring of methotrexate (MTX) after high-dose chemotherapy is pivotal for the accuracy of Leucovorin rescue**

Serum MTX concentration $\geq 42$ hours after start of infusion	Approximate Leucovorin dose required
50 $\mu\text{M}$	1,000 $\text{mg/m}^2$ every day 6 hrs (IV)
5 $\mu\text{M}$	100 $\text{mg/m}^2$ every day 6 hrs (IV)
0.5 $\mu\text{M}$	10 $\text{mg/m}^2$ every 3 hrs (IV or oral)
0.1 $\mu\text{M}$	10 $\text{mg/m}^2$ every 6 hrs (IV or oral)
< 0.05 $\mu\text{M}$	No modification
If $\geq 42$ hours MTX levels exceed 1 $\mu\text{M}$ , a high risk for toxicity has to be calculated.	

Moreover, TDM may provide insight into every day clinical practice, with regard to potential drug interaction such as smoking-related effects on irinotecan pharmacokinetics as well as individual non-adherence following oral cancer chemotherapy and dose optimization in special circumstances, e.g. dialysis. One should also consider the use of TDM to monitor significant impact of complementary or alternative medicine on anticancer drug pharmacokinetics, e.g. green tea extracts on sunitinib or tacrolimus plasma concentrations. TDM may also help to identify underlying pharmacogenetic disorders which would not normally be detected in time by routine practice. Recent results also suggest that TDM may be of increasing value in patients taking targeted therapeutic agents, for example, patients with chronic myeloid leukaemia or gastrointestinal stromal tumour in whom imatinib plasma levels must remain above 1µg/mL in order to improve tumour control [8].

### TDM in clinical oncology – cons

Although there are strong arguments in favour of TDM, there are good reasons why its application is not widespread and currently limited to intensified MTX regimens only:

(1) With the exception of MTX, there is no commercially available routine test system which means that TDM currently involves time-consuming analytical procedures such as LC-MS and HPLC. This may require an expensive combination of a broad range of

materials to be obtained and special staff training. Continuous validation and improvement of these analytical measures is mandatory to ensure standardization between different facilities. And particularly in the case of unstable products, long-standing analytical experience may be needed for the processing of probes.

(2) For most anticancer drugs, the boundaries of the therapeutic window are not as clearly defined as for carboplatin or 5FU. In addition, boundaries may vary from one indication to another and need to be confirmed by prospective randomized clinical trials.

(3) In most chemotherapy regimens myelosuppression represents the major dose-limiting toxicity which can be minimized by using blood products or cytokines in the following treatment cycle without the need for TDM. In addition, the optimization of treatment regimes involving novel agent is ongoing. For example, the use of taxane TDM may not be needed for non-small cell lung cancer (NSCLC) patients if cisplatin/pemetrexed is selected instead as the first-line regimen for patients with adenocarcinoma. TDM may be required for the oral administration of busulfan, whereas IV application is now routine practice in most cancer centres and is less likely to cause interindividual variations in drug plasma levels.

(4) Regarding clinical efficacy, TDM may not represent a pivotal tool because plasma levels may not accurately reflect the situa-

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**Table 2: Therapeutic drug monitoring in clinical oncology: pros and cons**

Arguments – pros	Arguments – cons
TDM may improve clinical outcome and tolerability	Besides MTX, no routine TDM assay is available
TDM may help to define and maintain a therapeutic window	Time- and cost-consuming implementation of analytical techniques
TDM may improve engraftment after high-dose chemotherapy followed by PBSCT	Therapeutic windows have to be prospectively defined
TDM may allow adherence control as well as identification of unexpected drug interactions	Ongoing change of treatment regimens, e.g. drugs, doses, administration routes Plasma levels may not reflect intratumoural phenotypes
TDM may allow individual dose optimization, e.g. dialysis	Genotyping appears to be preferred in the near future
TDM: therapeutic drug monitoring; PBSCT: peripheral blood stem cell transplantation	

tion in the tumour mass, owing, for example, to limited drug penetration into deeper compartments or the presence of multidrug resistance phenotypes. As a consequence, other diagnostic tools, e.g. PET-CT, or continuous tumour marker assessment may be more suitable than TDM [9].

(5) Over the last decade, genotyping has become a first-choice diagnostic tool: a single blood sample can provide a broad spectrum of information, such as the expression of cytochrome P450 isoenzymes. Many test systems are commercially available, producing rapid and standardized results. In addition, genotyping of predefined markers may be preferred to TDM for the monitoring of patients with pharmacogenetic enzyme disorders who may show individual sensitivity to drug-related organ toxicity, e.g. anthracycline-related cardiomyopathy in patients homozygous for CBR3 V244MG [10].

## Conclusion

Although most cytotoxic anticancer drugs have a narrow therapeutic window, TDM is not yet routinely established for many reasons, see Table 2. This is an unsatisfactory situation, however, given recently published data with 5FU TDM and correspondingly encouraging data in metastatic colorectal cancer patients. In addition, TDM may be of increasing importance during the use of novel targeted therapeutic agents to optimize their efficacy and tolerability during chronic treatment [11].

Moreover, phenotyping assays may be helpful as adjunctive information, for example, using either *CYP2D6* phenotyping with dextromethorphan as a probe in patients treated with Tamoxifen, or a CO<sub>2</sub> breath test with <sup>13</sup>C-Uracil before 5FU treatment. In these cases, phenotyping may be a closer indicator of TDM-proven drug levels than genotyping assays [12, 13].

In perspective, cancer centres specialising in the use of clinical pharmacokinetically guided treatment regimens may become preferred centres for patients and others based on the potential option to further improve clinical efficacy and tolerability of complex antineoplastic therapy.

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# Extended stability of rituximab, bortezomib and azacitidine for use in haematology

Extended stability of rituximab, bortezomib and azacitidine allows advance preparation with many benefits: a diminished or eliminated waiting time for the patient, a better organisation of the centralized unit and of the clinical ward and many cost savings.

## Introduction

The number of preparations of anticancer drugs has increased dramatically during the past two decades. In most cases, chemotherapy is administered to outpatients. However, the timely provision of chemotherapy is a constant challenge for hospital pharmacy aseptic units.

In the University Hospital of Brabois, France, we have up to 30 to 40 chemotherapy outpatients each day. Patients may have to wait for 2 or 3 hours for their drugs to be prepared from prescriptions issued on the day, a situation which is barely acceptable, and which also creates stress for pharmacy and nursing staff involved.

As the majority are haematology patients, and we are aware that advanced preparation of the most frequently prescribed drugs would diminish or eliminate patient waiting times, we decided to study how to prepare this in advance.

## The adaptation of the dose banding concept

Chemotherapy doses are commonly calculated according to the patient's body surface area (BSA), which is individually determined and so makes advance preparation difficult. However, more than 10 years ago, this criterion was questioned by UK teams who introduced the more flexible method of 'dose banding' to enable batch preparation of chemotherapeutic agents in advance [1].

Dose banding involves rounding up individual doses to predetermined standard amounts. A range of prefilled syringes or bags are prepared in advance and used to administer the doses. The patient receives one to four infusions or syringes. For example, an administration of 900 mg of fluorouracil requires three syringes (400, 300 and 200 mg). The maximum deviation permitted between the predetermined dose and the calculated dose is 5%.



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Because in our hospital, it is more convenient for nurses to administer just a single syringe or bag of a drug to an individual patient, we decided to adapt the dose banding concept.

We did so by keeping the same individually rounded doses but packaging these together into a single bag or syringe for administration to the patient. We focused our attention on three frequently prescribed drugs: rituximab, bortezomib and azacitidine.

Rituximab (Mabthera) is mainly used for the treatment of non-Hodgkin lymphomas. It generally requires IV infusion over 4 hours, but this can be reduced to 90 minutes for patients with good toler-

ance. The drug is administered before the CHOP treatment regimen with cyclophosphamide, doxorubicine and vincristine which is also delivered by IV infusion. The patient spends 6 or 7 hours in hospital, and so needs to begin the first infusion of rituximab as soon as possible.

A study carried out according to the ICH (International Conference on Harmonisation) Guideline Q5C has demonstrated a 6-month stability for the infusion in polypropylene bags [2, 3].

We obtain prescriptions in advance and prepare these one or two days before administration. The doses are standardized by physicians to be between 570 and 870 mg. For doses between 570 and 630 mg, we prepare a rounded dose of 600 mg; for doses between 630 and 690 mg, we prepare 660 mg, see Figure 1. Doses outside this range (below 570 mg or above 870 mg) and doses for clinical trials are prepared according to the BSA.

If treatment is cancelled or postponed, the infusion can be relabelled for use by a different patient according to a specialized procedure, see ISOPP, Chapter 20, Reuse of drugs [4].

Bortezomib (Velcade) is used for the treatment of myeloma and is administered intravenously over a few seconds on day 1, 4, 8 and 11 every 3 weeks. Older patients may have a regimen of weekly injections four times a month.

We have demonstrated stability of 5 weeks for a 1 mg/mL bortezomib solution in 0.9% sodium chloride stored at 2°C–8°C [4, 5]. We kept the same organisation as for the rituximab infusions: prescription in advance and standardization of the syringes between 1.5 and 2.7 mg, see Figure 1. The maximum deviation between administered and calculated doses should be no more than 6.6%, according to the BSA.

Azacitidine (Vidaza), is indicated for the treatment of myelodysplastic syndromes and acute myeloid leukaemia. The drug is given as SC injections daily for one week. The manufacturer indicates stability as a suspension of 25 mg/mL for only 45 minutes at room temperature, 8 hours in the refrigerator and 22 hours if the lyophilisate is reconstituted with refrigerated water for injection.

We have demonstrated in the stability study that for advance preparation, a solution of azacitidine can be stored frozen at -20°C for 8 days, and for 8 hours at 2°C–8°C after thawing at room temperature for 45 minutes [6].

All the syringes are prepared in advance one or two days before the administration. The syringes are thawed at room temperature at 09:00 and sent to the wards one hour later in a cold box with an expiry time of 17:00 the same day.

The standardization of the syringes is between 47.5 and 77.5 mg, see Figure 1.

patients when necessary except for azacitidine after thawing, which is mandatory with costly drugs. After two years experience with frozen azacitidine and one year with refrigerated rituximab and bortezomib, we have lost only five azacitidine syringes and no bortezomib syringes although 4% of bortezomib syringes were cancelled owing to the common neurotoxicity of this drug. Very few rituximab infusions were cancelled and none were destroyed.

Advance preparation of these three drugs is done during the afternoon, outside the hours of highest activity. Advance preparation of prescriptions has many benefits:

- a decrease in patient waiting times
- reduced stress for pharmaceutical and nursing staff, minimisation or elimination of drug wastage.

Our objective is now to extend this arrangement to anticancer drugs used for gastroenterology patients (oxaliplatin, irinotecan and fluorouracil).

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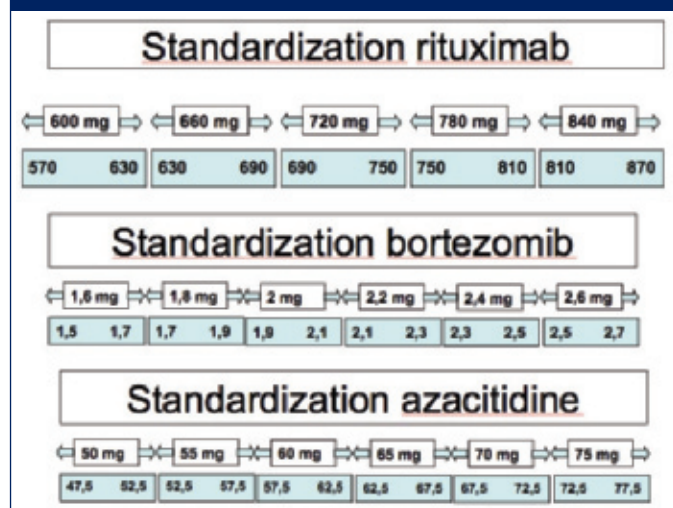
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**Figure 1: Standardization of commonly used doses of rituximab, bortezomib and azacitidine**



In these three examples, the most prescribed doses are standardized with the agreement of physicians. The extended stability gained allows drugs to be re-assigned to different

# The use of bar codes in hospitals – a pharmaceutical perspective

The identification of medication at the moment of administration has been an issue for a long period of time. Identifying bar codes provide an assurance that the right medication has been given to the right patient.

## Background of bar codes on packages

The Dutch Association of Hospital Pharmacists (NVZA) has recommended that all deliverable medications should be formulated in unit-dose cells (EAGs).

It is vital that all EAGs contain an identifying bar code. This will provide a registerable electronic guarantee that the right medication has been given to the right patient [1].

EAGs are single unit packages of varying formulations, e.g. oral tablets or capsules; liquid-containing ampoules, syringes, or vials; ointments, etc. EAGs are normally labelled with the following information:

- non-proprietary and proprietary names
- dosage form
- strength
- expiration date
- control number (lot number)
- bar code that has a unique number called a GTIN (global trade item number).

The inclusion of a bar code is vital. European Association of Hospital Pharmacists (EAHP) [2] and the American Society of Health-System Pharmacists (ASHP) [3] have recommended that unit-dose formulations are available for every hospital-administered drug, and that these drugs should have identifying bar codes.

To better understand the necessity for an identifying bar code, a short explanation of the processes involved are now discussed.



Bas Drese

## Prescription to administration

In the prescription-administration process there are two kinds of logistic: the virtual logistic, i.e. the process involved with the ordering of the medication; and the tangible logistic, i.e. the process involved when the drug is administered to the patient, see Figure 1.

These two logistical processes come together when the nurse is administering the drug to the patient. At that moment, the patient, the medication and the information about the patient's prescription must be matched, not only visu-

ally by the nurse, but also by the electronic bar code identification system. To satisfy this process, a few solutions have been introduced. These will be discussed in the remainder of this article.

## Cabinets

Cabinets are computerised ward stocks connected to the pharmacy-system/CPOE-system. The cabinet only allows the medication to be available to the nurse at the time of administration. These machines are always up to date and can handle all packaging. However, they can be located quite a distance away from the patient, meaning that the administration check–medication overview–cannot be reviewed in the patient's presence. In addition, when a medication is not packaged in unit doses, the nurse is sometimes required to administer multiple doses of the same

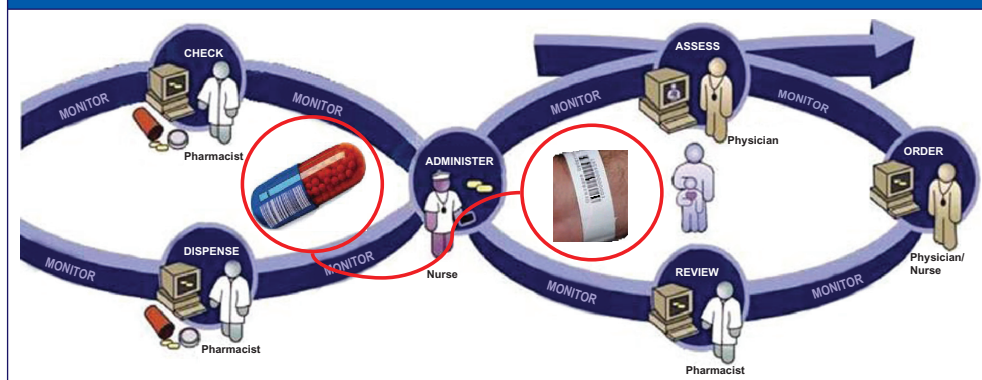


medication at the same time. This could lead to mix-ups. From a financial perspective, the total cost of ownership of the cabinets is relatively high, but the handling costs are relatively low.

## Patient-specific logistics, manual

In this system, the medication is made patient-specific by putting it in a patient-drawer in a mobile cart. This is done by either the pharmacy department or the nurses. A paper form of the medication overview is

**Figure 1: Integration of virtual and tangible logistical processes during the prescription-administration stage**







available on the cart. The system is able to handle all packaging, and providing it is labelled correctly the nurse is able to check the medication. However, preparation of the cart is time-intensive, and errors can be made, particularly if staff are inexperienced or inadequately trained. The total cost of ownership of a cart is low, the handling costs are high.

### Patient specific logistics, using FDS

The medication is made patient-specific in the pharmacy by an FDS machine which places the medication in a small plastic bag labelled with patient identification and medication content. The major problem with this method is that when more than one tablet is bagged, a change in medication (stop or dose change) cannot be managed by the nurse because the different tablets are unidentifiable. If tablets are packed one by one, this method is very expensive, as additional packaging materials and ink ribbons are costly. Only tablets and capsules are supported in most FDS systems, although separate FDS systems are available which can distribute ampoules and infusion bags. The total cost of ownership of the cabinets is relatively high, the handling costs are relatively low.



### Patient specific logistics, using BAP

A solution that is flexible and safe is a cabinet-like solution which is on wheels and allows adequately bar-coded medication to be brought directly to the patients' bed. In The Netherlands, such apparatus is known as a BAP-cart, (bed-side assortment picking). This apparatus is able to handle all types of packaging, but requires an adequately identifiable (preferably bar-coded) cell package. The total cost of ownership of the carts is relatively low, the handling costs are also low.



### Prescription to preparation for injection/infusion

Having adequate packaging and labelling is also crucial during the preparation of parenteral medication. Although most preparations in The Netherlands are made on the ward by the nurse, there is an increasing awareness that preparing these medications in the pharmacy would be more beneficial. This will help to avoid mix-ups, which would be difficult to detect at a later stage. Compared to medications that are synthesised on the ward, pharmacy-prepared medications are synthesised under more aseptic conditions. This would usually mean that a second person is required to check the identification and amounts of compound used. However, when an identifying bar code is present on each compound, the control could be efficiently performed using an electronic bar code scanner, computer software, and a mechanical scale.

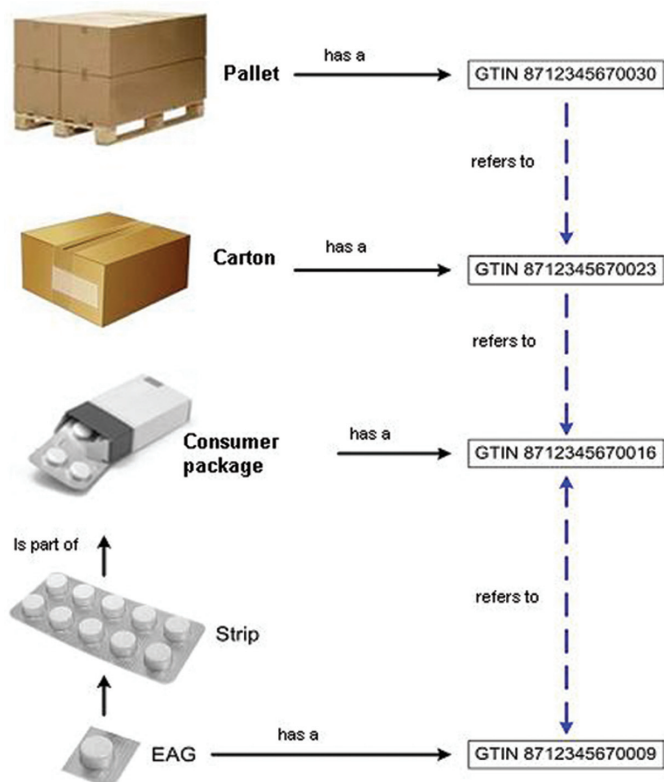


### Current status

To date, there has been little progress in creating a uniform identifying bar code system on primary packaging.

One of the reasons that the pharmaceutical industry has not adjusted their packaging to the standard requested by FDA, ASHP, EAHP (and NVZA), may be that each market has different requirements, e.g. the product identification number. This would make any individual packaging updates costly.

Another issue for the pharmaceutical industry is the space required for a bar code on a small unit-dose package. This problem is also recognised by FDA, 'The pertinent labelling regulations present problems in interpretation in that they are inconsistent with respect to exemptions for containers too small or otherwise unable to accommodate a label with sufficient space to bear all mandatory information. As a result of several



recent regulatory actions emphasizing these inconsistencies, the regulations will be rewritten in the future to clarify the requirements' [4].

These issues combined with a lacking sense of urgency in the hospitals mean that stakeholders are still waiting for developments. Some hospitals developed workarounds, e.g. in-house re-labelling of the medication, but these actions generally proved problematic. Some industries print a bar code on their primary package, but the presence of an identifying bar code is still rare.

Hopefully the following developments can make the difference:

- GS1 has developed a global standard for identifying medication on each possible level of packaging. The pharmaceutical industry is urged to comply with this standard. The interest of the industry for a global identification number is that it has cost-saving potential in B2B logistics and helps to avoid counterfeit. A new two-dimensional way of presenting a bar code has become possible where the limited amount of space

on the cell is no longer an issue. This makes it possible to have one primary package for each product for (almost) the entire world.

- Patient safety is a rising topic in the boardroom of hospitals and pharmaceutical companies.

## Conclusion

It should be possible to develop a type of packaging which is user-friendly to hospital staff, enhances patient safety, and provides sufficient incentive to the industry to develop it. With this in mind, the NVZA has initiated dialogue with the pharmaceutical industry to address and discuss this issue and promote EAG packing.

We recommend that for all levels of packaging including EAGs, industry should:

- obtain GTINs
- print GTINs on their product bar codes
- include Lot numbers and expiry dates
- produce labels which are uniform in layout.

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## Circulating knowledge: an oncology pharmacist improves quality in patient care

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# Circulating knowledge: an oncology pharmacist improves quality in patient care

One of the central Asian countries, Kazakhstan—as big as Europe with only 16 million people—is looking for western-level health care. An intrepid oncology pharmacist reports how she introduced new equipment and new management perspectives to a university hospital and made many friends.

## Introduction

In July 2009, the WHO identified priority areas in Kazakhstan health care. Finally a project ‘Support for maternal and child health in Kazakhstan’ started, supported by the EU with Euros 1.2 million from the EU budget.

I got a call at the end of January 2011, ‘Are you willing to support the WHO/EU project to improve children’s health in Kazakhstan?’ [1].

Although I am flexible, I thought I heard somebody else answering: ‘YES! When do you need me?’ ‘As soon as possible: nothing to do with medicine functions, even if we have some medicines, sometimes we cannot even do surgery, so babies lose limbs; there is no communication between the healthcare team and most parents have to arrange medicines for their kids from abroad (Russia or Turkey).’

So I found myself on a plane to Astana, the new capital of Kazakhstan, on 28 February 2011. Reading one of the travel magazines, I realised that I could not identify neighbouring countries/regions Afghanistan, Kirgizstan, Mongolia, or Uzbekistan. I finally found Astana on the map, the next biggest city in the north was Novosibirsk and to the south lay the Hindu Kush Mountains.

## First impressions

When I got out of the plane I had problems breathing, it was -49°C and I was overwhelmed both by the temperature and the endless taiga.

I was driven directly to the hospital to meet the CEO who told me about the ‘bad pharmacy’ which was definitely guilty of everything. Listening politely I asked him if I might make my own picture and visit my colleagues. I got my translator, Natalja, and guess what: Kazakhstan is just like other places—the pharmacy is far away from the wards, close to the kitchen and in the cellar.

Before showing me round, the Chief Pharmacist asked: ‘Are you a colleague or a spy?’ I asked: ‘Do you expect a spy to spend her holidays in Astana in winter? If you want your professional life to improve, give my translator a call!’

As expected I was invited to visit the hospital pharmacy the next day. The amount of space was impressive and my imagination took flight. But the space was just to store medicines that ran out



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of stock. I have never felt so frustrated, but to be polite I could not show any reactions.

## The situation in Kazakhstan

In 2011, 368.9 billion tenge (Euros 1.9 billion) were provided for the Kazakhstan healthcare sector [2]. Over 10,000 pharmaceuticals are currently registered there. Looking at the list with my translator, I found out within two minutes that not a variety of drugs but dosage and dosage form make this number, and that they do not meet the WHO list of essential medicines for children.

The government grants tenders to its own company which is responsible for buying and distributing medicines. In Europe you get medicines within hours if urgent. Pharmacies in Kazakhstan sometimes wait for months. In these situations families get into debt to obtain basic medicines for their children. When morphine runs out, children may lose limbs or die of sepsis, because surgery is impossible.

President Nazarbayev’s target is to source 50% of medicines, in volume terms, domestically by 2014, although the country has major regulatory gaps. One problem is the absence of local good manufacturing practice (GMP) standards, despite a 2014 GMP compliance deadline. Another is a formulary system [3].

Interestingly, mortality due to cancer is similar to that in western countries, despite the lack of modern chemotherapy. However, life expectancy for men is 63.24 years, for women 74.24 years, about 13% less than in Europe [4].

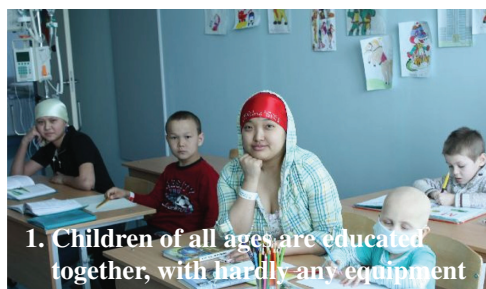
## Finding the problems

They produced ‘sterile’ solutions for neonates under conditions I could not have imagined. When I asked them about their hood, they did not understand, because in Kazakhstan it is the nurse’s job to prepare cytotoxic preparations. So, I asked them to tell me what they do when cytotoxic substances spill. They wipe with paper towels and then place them into the domestic rubbish.

Nobody wanted to accompany me to the haemato-oncology ward, another taboo: pharmacists do not visit the wards. Realising this also applied to me, I had to wait a day to get written permission from the medical director to visit all wards and have access to patient data.

Next day when I went there, they showed me the children’s lessons, to distract me from the ward, see photo 1.





1. Children of all ages are educated together, with hardly any equipment

Because I had permission, they had to let me see the ward. I saw children with leukaemia who received a proton pump inhibitor and

cortisone, because there was no medicine. Nurses prepared the cytotoxics at the bedside. There were no algorithms for supportive care. And when I asked them to show me their refrigerator I was simply shocked at the lack of medicines.

## Teamwork starts

Suddenly I heard German! Dr Aigul Brimova had won a scholarship and graduated at the University of Hannover, where she did her thesis in neoangiogenesis in solid tumours before and after chemotherapy. She said: 'Oncology and cancer know no borders, no language, we have to work together to provide supportive treatment and patient education so our patients don't lose courage.' She was open and happy to speak German again.

So, I asked her if she could imagine working together with a pharmacist. She answered: 'Sure, because patient safety is at the centre and I miss the healthcare team I was used to in Germany.' So, I went back to the pharmacy and asked if anyone was willing to cooperate with the ward, starting slowly but be present and try to learn as much as possible. The first question was 'Do we get milk?' At first, I thought I had misunderstood, but the translator explained that in the former Union of Soviet Socialist Republics people working with hazardous substances got condensed milk each day. Sensitised by revelations about the primary testing venue for the Soviet Union's nuclear weapons in Semipalatinsk people are afraid of what-ever might cause cancer.



2. Physicians and pharmacists start to work as a team

To their disappointment—no milk. Then they asked me if they could ever get pregnant (again). Despite their reservations, I persuaded a young pharmacist to meet Dr Brimova the next day, see photo 2.

I decided to offer training in sterile glove usage, spill kit and extravasation. My foreign colleagues told me not to expect anybody to take part. It was a pleasure: the whole pharmacy, the oncology nurses and physicians attended. We ran out of chairs, people had to stand, but they stayed to the very end. I had to repeat the training sessions many times over several visits. Theatre nurses also wanted training in sterile gloves, see photos 3 and 4.



3. Training in sterile gloves



4. My translator Natalja who is a perfect spill kit teacher now



5. Now we can get started: a hood

## Building on trust

Sensibilised by all my training they made it happen: I was proudly presented with a hood five weeks later, see photo 5.

This was the moment when I knew we could take the next steps, because they trusted me.

I went to that 500-bed university children's clinic six times in 2011, with a mission to 'improve the management of a hospital pharmacy, establish quality guidelines, implement treatment algorithms and multidisciplinary education in pharmacology.' We went through an American hospital accreditation programme—Joint Commission International (JCI) accreditation: pharmacy passed well, also oncology and we are waiting to hear if the first university clinic in central Asia will become JCI accredited after a focussed survey end of February. I am very proud of all those who were so eager to learn and put their trust in me.

Child mortality in Kazakhstan is one of the highest worldwide. To ensure quality will require a complete change in health culture and a step towards western standards. Supervision needs to be combined with training to ensure guidelines are implemented, financial mechanisms need to be revised to avoid incentivising inappropriate practices and to reward virtuous practices such as reduced admission rates, short stays, effective drug supply and appropriate use of drugs. Pharmacy without quality management—especially in oncology services—is unacceptable.

Photo credit: courtesy of Dr Doris Haider

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# Stability of Hospira filgrastim following changes to thermal and photic storage conditions

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## Abstract

**Study objectives:** Protein-based medicines have specific storage requirements to ensure chemical stability and purity, but exposure to different environmental conditions can occur in normal use. The effect of extended unrefrigerated storage and thermal cycling on the stability of Hospira filgrastim (Nivestim) was examined.

**Methods:** Three batches of two presentations of Hospira filgrastim prefilled syringes (30 MU and 48 MU) were kept refrigerated until 1–8 months after expiry. After this period, the samples were exposed to either three cycles of storage at  $25 \pm 2^\circ\text{C}$  and  $5 \pm 3^\circ\text{C}$ , seven days at  $25 \pm 2^\circ\text{C}$  in light or dark conditions, three cycles at  $25 \pm 2^\circ\text{C}$  and  $5 \pm 3^\circ\text{C}$ , followed by seven days at room temperature (light and dark), or frozen for three days. Expired control samples were maintained at  $5 \pm 3^\circ\text{C}$ . Samples were analysed for appearance, pH, particulate matter, protein concentration, impurities, biological activity and sterility.

**Results:** All of the parameters measured for each sample of Hospira filgrastim were within the shelf life specification requirements, and there was no qualitative difference between parameters measured in samples that had undergone environmental stressing versus those maintained at  $5 \pm 3^\circ\text{C}$ .

**Conclusion:** Hospira filgrastim formulations are unaffected by cyclical changes in temperature between the fridge and  $25 \pm 2^\circ\text{C}$ , and are also unaffected by exposure either to room temperature for seven days or to freezing for three days. Therefore, physicians, pharmacists and patients can be confident that Hospira filgrastim remains active and stable during environmental excursions commonly encountered in general use.

**Keywords:** Filgrastim, G-CSF, refrigeration, stability, temperature

## Study objectives and introduction

Neutropenia is a frequently occurring complication of myelosuppressive chemotherapy [1]. Neutropenia results in increased susceptibility to infection [1, 2] and can require treatment with anti-infectives. Patients with neutropenia are frequently admitted to hospital, and the condition can also require modification of chemotherapy regimens with the potential to compromise therapy outcomes [2]. The mainstay of therapy for neutropenia is recombinant granulocyte colony-stimulating factor (G-CSF, r-metHuG-CSF, rHuG-CSF, filgrastim) a cytokine that stimulates proliferation of haematopoietic progenitor cells that form mature neutrophils [3].

The manufacturing and formulation of biopharmaceuticals has inherent variability arising from differences in cellular expression systems and other manufacturing details. Recently, biosimilar filgrastims have become available. Recognising the variability in biopharmaceutical manufacture, EMA has issued guidance on standards that must be met for biosimilar filgrastims to obtain regulatory approval for medicinal use [4–7]. These standards are far more stringent than those required for approval of small molecule drugs, and include the requirement to conduct comprehensive assessments of quality, activity and clinical effectiveness [4–7]. In accordance with EMA requirements, the biosimilar Hospira filgrastim (Nivestim) has been studied in a development programme that included preclinical studies, two phase I clinical trials and one phase III clinical trial. The preclinical and phase I studies demonstrated the pharmacodynamic and pharmacokinetic equivalence of Hospira filgrastim versus its reference product Amgen filgrastim (Neupogen) [8–10].

The phase III study confirmed the bioequivalence of Hospira filgrastim and Amgen filgrastim in a randomised, multi-centre trial of 279 patients undergoing myelosuppressive chemotherapy [11]. In the phase III study, Hospira filgrastim exhibited a manageable safety profile. The most common adverse event was bone pain, which is also the same for Amgen filgrastim [11].

As a result of these clinical trials, Hospira filgrastim gained approval for the treatment of neutropenia and the prevention of febrile neutropenia in cancer patients treated with cytotoxic chemotherapy (except those with myelodysplastic syndromes and chronic myeloid leukaemia) [12]. Hospira filgrastim is also indicated for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy to support bone marrow transplantation, for the treatment of neutropenia in patients with human immunodeficiency virus, and for the treatment of severe congenital, cyclic or idiopathic neutropenia [12].

All protein-based biological medicines require careful handling and storage, to ensure chemical stability and to maintain a long shelf life. However, there is a need to understand what degree of flexibility exists regarding storage parameters, so that physicians can have the confidence to administer drugs that have been exposed to different environmental conditions, and so that healthcare teams can offer practical advice to patients on storage and handling. Therefore, a biochemical characterisation study was conducted to explore the effect of extended unrefrigerated storage, thermal cycling and freezing on the stability of Hospira filgrastim.

## Methods

This study tested two formulations of Hospira filgrastim: the 30 MU (300 µg/0.5 mL) prefilled syringe, and the 48 MU (480 µg/0.5 mL) prefilled syringe. The third presentation of Hospira filgrastim is 12 MU (120 µg/0.2 mL), which is an under-filled version of the 30 MU presentation, and was not tested in these experiments.

Three batches of each of the two presentations were kept in refrigerated storage (2°C–8°C) for 31–38 months from manufacture (refrigerated shelf life 30 months). After this period, the samples were subjected to four types of environmental excursion:

1. Cyclic test. Samples were stored for 2 days at  $25 \pm 2^\circ\text{C}$  (hereafter referred to as  $25^\circ\text{C}$ ), followed by 2 days storage at  $5 \pm 3^\circ\text{C}$  (hereafter referred to as  $5^\circ\text{C}$ ). This storage pattern was repeated three times (cycles) for each sample.
2. Seven days at room temperature. Two sets of samples were exposed to seven days at room temperature ( $25^\circ\text{C}$ ), one set was exposed to light, and the other set was kept in the dark (wrapped in aluminium foil).
3. Cyclic test, followed by seven days at room temperature. This test involved the cyclic test, followed by seven days exposure to room temperature ( $25^\circ\text{C}$ ), again with one set of samples exposed to light and the other set wrapped in foil.
4. Freezing test. Samples were exposed to  $-20 \pm 5^\circ\text{C}$  (hereafter referred to as  $-20^\circ\text{C}$ ) for three days before returning to standard refrigerated storage.

Each sample was analysed for physicochemical characteristics, chemical purity and biological activity, see Table 1. Physical appearance was assessed visually. pH and particulate matter were measured in accordance with the *European Pharmacopoeia* 6.8 [13]. Protein concentration was measured spectroscopically using the method established by Groves et al. [14, 15].

Each sample was tested for protein impurities. The battery of tests used were designed to detect all protein species that differ from filgrastim, including misfolded, oxidised and dimeric forms, which are known to occur when filgrastim degrades. The quantity of all impurities in each sample was determined via sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), size-exclusion high-performance liquid chromatography (SEC-HPLC), isoelectric focussing (IEF), reverse phase HPLC (RP-HPLC) and ion chromatography (IC). For SDS-PAGE, samples were separated on a 13% polyacrylamide gel under reducing and non-reducing conditions according to methods set out in the *European Pharmacopoeia* 6.8 [13]. The required standard for SDS-PAGE was that the principal silver-stained band in the electropherogram obtained with the test solution should be similar in position to the principal band obtained with the reference solution, Filgrastim Reference Substance 1920, which is an in-house standard calibrated against the international standard of G-CSF 88/502. Molecular weights should be between 14–21 kDa using standards from

**Table 1: Methods of analysis and required standards**

Method	Acceptance criteria	LLOQ
<b>Physical and chemical parameters</b>		
<b>Appearance</b>		
<b>Visual</b>	A clear, colourless solution	–
<b>pH</b>		
Ph. Eur. method	3.8–4.2	–
<b>Particulate matter</b>		
<b>Visible</b>		
Ph. Eur. method	Practically free from visible particles	–
<b>Sub-visible</b>		
Ph. Eur. method	Practically free from visible particles	–
$\geq 10 \mu\text{m}$	$< 6,000$ particles/syringe	–
$\geq 25 \mu\text{m}$	$< 600$ particles/syringe	–
<b>IEF</b>		
Ph. Eur. method	Reference solution 10%*	–
<b>SDS-PAGE</b>		
Ph. Eur. method	Test solution 2%*	–
<b>Purity</b>		
<b>SEC-HPLC</b>		
Ph. Eur. method	Impurities with molecular masses higher than that of filgrastim should not constitute more than 1.0% of the sample	0.20%
<b>RP-HPLC</b>		
Ph. Eur. method	Any individual impurity should not be more than 2.0%. Total impurities should not constitute more than 3.5% of the sample	0.20%
<b>IC</b>		
In-house method	f-met filgrastim and more acidic-related impurities should not constitute more than 1.0% of the sample	0.20%
<b>Potency</b>		
<b>Biological assay activity</b>		
Ph. Eur. method	$0.9 \times 10^8$ – $1.5 \times 10^8$ IU/mg of protein	–
<b>Protein concentration (UV/VIS)</b>		
48 MU	0.86–1.06 mg/mL	–
30 MU	0.54–0.66 mg/mL	–
<b>RP-HPLC assay</b>		
48 MU	0.86–1.06 mg/mL	–
30 MU	0.54–0.66 mg/mL	–

(Continued)



**Table 1: Methods of analysis and required standards**

Method	Acceptance criteria	LLOQ
<b>Bacterial endotoxins</b>		
Ph. Eur. method	< 40 IU/mg	–
<b>Sterility</b>		
Ph. Eur. method	Sterile	–
<p>*No band is more intense than the principal band in the electropherogram obtained with the solutions.</p> <p>LLOQ: lower limit of quantitation; Ph. Eur.: European Pharmacopoeia 6.8 [13]; IEF: isoelectric focussing; SDS-PAGE: sodium dodecyl sulphate polyacrylamide gel electrophoresis; SEC-HPLC: size exclusion high performance liquid chromatography; UV/VIS: ultraviolet-visible spectroscopy; RP-HPLC: reverse phase HPLC; IC: ion chromatography.</p>		

GE Healthcare, or between 14.4–21.5 kDa using standards from Bio-Rad.

An IEF system (GE Healthcare) was used to determine the isoelectric point for each sample, and for detection of impurities with isoelectric points differing from that of the reference filgrastim. Samples were separated on an IEF gel containing 6% acrylamide and 3 M urea. The pH gradient was 4.0–8.0, and proteins were visualised with Coomassie Brilliant Blue R-250 [13]. The required standard for IEF was that the principal band in the electropherogram obtained with the test solution should be in a similar position to the principal band in the electropherogram obtained with the reference solution.

The SEC-HPLC method was used to determine impurities with molecular masses higher than that of filgrastim, and was based on the method published in the *European Pharmacopoeia* 6.8 [13]. SEC-HPLC was performed using an Agilent HPLC machine equipped with a diode array. Separation was achieved using a silica-based column from Tosoh Bioscience (TSKgel G3000SWXL; 7.8 × 300 mm; 5 µm); using a flow rate of 0.5 mL/min. Lower limit of quantitation (LLOQ) for SEC-HPLC was 0.20%.

The quality of the filgrastim assay and degradation products in each sample was determined via RP-HPLC using the method published in the *European Pharmacopoeia* 6.8 [13]. Reverse phase high-performance liquid chromatography analyses were performed on the same machine used for SEC-HPLC, but with a Phenomenex Jupiter C4 column (4.6 × 250 mm; 5 µm) with a linear 60 min gradient of acetonitrile in 0.1% trifluoroacetic acid, and a flow rate of 0.6 mL/min.

f-met filgrastim, an established degradation product of filgrastim, and impurities with greater acidity than filgrastim were determined via IC using an in-house method. Analyses were performed on an Agilent fluorescence HPLC, and separation was achieved using a Tosoh Bioscience TSKgel SP-5PW column (7.5 mm × 75 mm; 10 µm) with a methacrylic polymer stationary phase, an n-propyl-sulphonate functional group

and a 20 min linear gradient. The mobile phases were sodium acetate trihydrate 0.02 mol/L (pH = 5.4) and sodium chloride 0.5 mol/L, with a flow rate of 1.0 mL/min.

Potency was assessed according to the *European Pharmacopoeia* standards [13] via a validated biological assay in M-NFS-60 murine myeloblastic cells. The required standard was  $0.9 \times 10^8$ – $1.5 \times 10^8$  IU/mg total protein in the sample. Sterility was assessed using a membrane filtration method. Concentrations of bacterial endotoxins should remain < 40 IU/mg.

All methods used for product quality control were validated in accordance with International Conference on Harmonisation guidelines. Analysis methods, required standards and LLOQ are shown in Table 1.

## Results

There were no significant differences in filgrastim concentrations between samples undergoing environmental excursions with those maintained at 5°C. Protein concentrations and filgrastim assay remained within specified limits derived from requirements of drug regulatory authorities (filgrastim assay limits: 0.54–0.66 mg/mL for 30 MU samples and 0.86–1.06 mg/mL for 48 MU samples; see Figure 1). Biological potency was also maintained in all samples, and remained within the pre-specified limits of  $0.9 \times 10^8$ – $1.5 \times 10^8$  IU/mg of protein, see Figure 2.

All samples were clear and colourless, in-line with the required specifications of Hospira filgrastim, and the pH of all samples was in the range 4.0–4.1, also in line with the required specification, see Table 1. No particles were visible in any tested samples, and all results complied with requirements for sub-visible particulate matter ( $\leq 6,000$  particles  $\geq 10$  µm and  $\leq 600$  particles  $\geq 25$  µm per syringe, see Table 1).

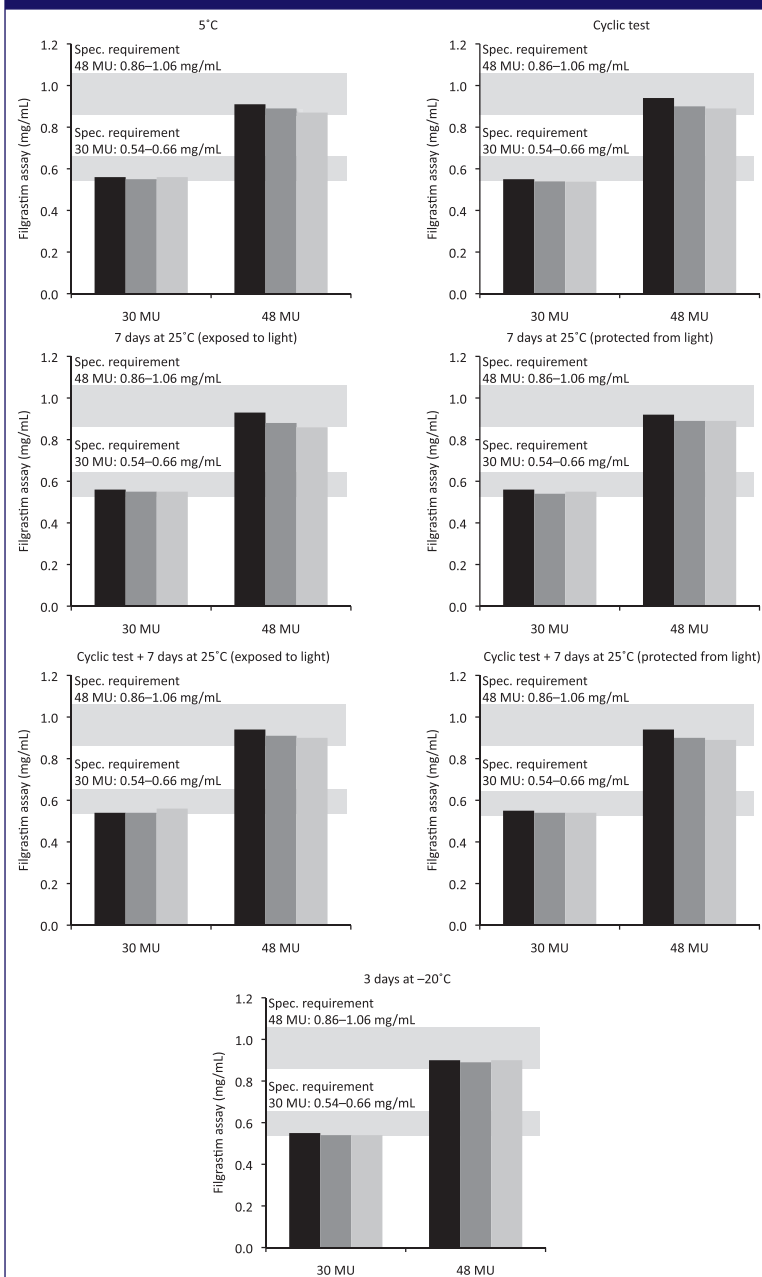
Data from SDS-PAGE, IEF, RP-HPLC, IC and SEC-HPLC showed no evidence of impurities beyond the required ranges, see Table 2. The quantities of f-met filgrastim impurities and impurities of greater acidity than filgrastim, were slightly higher in 30 MU samples stored for seven days at room temperature following thermal cycling, than in samples stored continuously at 5°C; however, all concentrations remained below the 1.0% specification limit, see Table 3.

Bacterial endotoxin levels remained below 40 IU/mg (specific limit for Hospira filgrastim limit based on total daily dose in patients) in all samples and no microorganism contamination was evident following environmental variations.

## Discussion

The therapeutic efficacy of protein-based medicines is dependent on the conformational structure of the protein molecule. However, proteins are complex, flexible structures and are sensitive to external environmental conditions [16]. Degradation of concentrated proteins in storage is generally caused by inter- and intra-molecular reactions such as hydrolysis, deamination,

**Figure 1: Filgrastim assay in time-expired batch samples of Hospira filgrastim exposed to varying environmental conditions**



Following 30 months of storage at 2°C–8°C, batches of Hospira filgrastim 30 MU and 48 MU were exposed to a range of environmental conditions and assayed for filgrastim concentration. Values represent absolute filgrastim assay in each sample (mg/mL). Shaded bars represent each sample from a given batch of Hospira filgrastim. Horizontal shading represents the required specification for filgrastim assay in each presentation. Spec: specification.

oxidation, aspartate isomerisation and aggregation [17]. Aggregation is the principal means by which all high-concentration proteins degrade, and can occur in response to changes in thermal conditions that affect conformational structure [17]. Various methods are now routinely used to combat aggregation. Lyophilisation is used to restrict protein mobility—lyoprotectants can also be added [17], and there is evidence that the specific molar ratios of stabilisers is important for successful lyophilisation [18]. For aqueous protein solutions, osmolytes, e.g. sugars, can be introduced to the formulation; these are excluded from

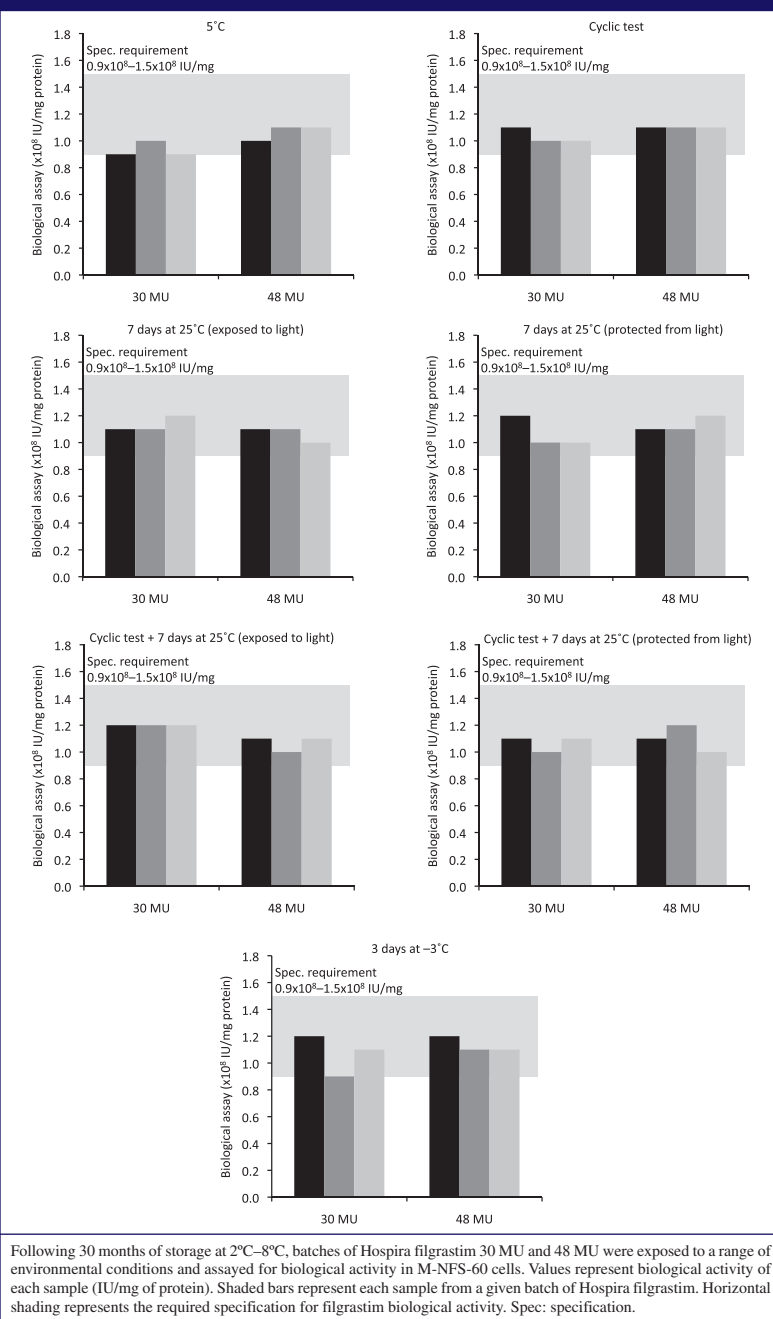
the immediate protein microenvironment and are preferentially hydrated [17].

The chemical characterisation and formulation of filgrastim continues to be a topic of research to better understand the chemistry and stability of the product, and to ensure a safe and efficacious molecule [19]. Ultra-high throughput computational screening methods have been used to identify large numbers of G-CSF variants with different stability profiles. Using these methods, Luo et al. screened  $10^{21}$ – $10^{28}$  G-CSF sequences that were based on alterations to 25–34 residues deep in the protein filgrastim core [20]. Optimal core designs were selected for biochemical and pharmacokinetic characterisation and efficacy testing. This process was able to identify filgrastim variants with long-term stability at temperatures as high as 13°C with 5–10-fold improvements in shelf life without the loss of biological activity [20].

Recent research efforts, such as high throughput screening, have yet to result in the generation of a G-CSF with improved storage requirements; however, the inherent stringency of EMA requirements for the development of European biosimilar G-CSFs [4–7], means that the required standards for the quality of the molecular and formulated products are the same as that of the originator. The guidelines issued by EMA that govern the requirements must be met for approval if biosimilars differ from the requirements set out for small molecule therapeutics. For small molecule weight drugs, e.g. chemotherapeutics and other non-protein drugs, demonstration of pharmacokinetic similarity is sufficient to gain approval; however, EMA recognises that the complexity of the manufacturing processes for protein therapeutics results in inherent variability in the final synthesised product. Therefore, therapeutic equivalence is difficult to determine without full-scale clinical trials [21]. With these issues in mind, EMA has issued strict guidance on the standards that must be met by original protein therapeutics and their biosimilar counterparts to obtain approval for therapeutic use in humans [4–7]. For follow-on biologics, these standards must be met in order for the drugs to be termed ‘biosimilar’. The EMA guidelines ensure therapeutic efficacy, protect patient safety and minimise the effects of inter-batch variability. The guidelines include the consideration of shelf life of the reference product and provide recommendations on the standards that must be met by any analytical techniques used [5].

The data presented in this study have demonstrated that Hospira filgrastim, a biosimilar G-CSF, can be exposed to cyclical changes in temperature between 5°C and 25°C (mimicking temperature excursions during transport and handling), exposure to 25°C for seven days or frozen for three days. All of the tests were done after the nominal expiry date of the product (30 months). Notably, no increases in the quantity of impurities with molecular

**Figure 2: Biological activity of Hospira filgrastim in time-expired batch samples exposed to varying environmental conditions**



weights higher than filgrastim were observed, thus demonstrating that none of the environmental alterations employed, resulted in aggregation. On the basis of these findings, the SmPC for Hospira filgrastim has been updated to inform pharmacists and physicians that they should not be concerned about exposure of Hospira filgrastim to room temperature conditions for a single period of seven days. While the drug can be used at any point during this time, it should be discarded at the end of the seven days. Although we did not test the 12 MU formulation of Hospira filgrastim, this is a smaller presentation of the same master batch as the 30 MU presentation; therefore, data collected on the 30 MU syringe can

be extrapolated to the 12 MU syringe. Hospira continues to test formulations of its filgrastim presentations, to further define their stability characteristics.

The data presented here, and the update of the SmPC for Hospira filgrastim that was based on them, provide genuine practical benefits for patients receiving G-CSF, to support myelosuppressive chemotherapy. For instance, many courses of G-CSF therapy are 3–5 days in duration [22], commencing 24–72 hours after the end of the chemotherapy cycle [23, 24]. Therefore, under the updated storage instructions for Hospira filgrastim, the drug does not require refrigerated storage after dispensing from the hospital pharmacy at the time of patient discharge, as long as the drug is used within seven days. This may be beneficial to patients who lack reliable refrigerated storage space, or those who are planning extended periods away from home; however, refrigeration should be used for G-CSF courses lasting for six days or more, or for regimens that require commencement of G-CSF therapy more than 24 hours after dispensing of Hospira filgrastim in the cycle [25].

In addition to obtaining data to support 7-day, out-of-fridge stability for Hospira filgrastim, the present study also gathered data demonstrating Hospira filgrastim is unlikely to be affected by accidental freezing or thermal cycling between 5°C and 25°C. The environmental conditions to which Hospira filgrastim was exposed to in the present study, reflect many of the genuine thermal variations that drugs can undergo in storage and transport, and the resulting data provide much needed confidence that frequently encountered changes in environmental conditions do not affect the stability or biological activity of Hospira filgrastim. These data are significant in the field, as they represent a step towards stability data gathered with the aim of improving patient compliance and ease of use, rather than investigating stability from a purely technical or commercial standpoint.

The 7-day, out-of-fridge stability at room temperature, is an important addition to the existing user-centred features for Hospira filgrastim, that include prefilled syringes with integrated needle-safe devices, a wide-range of presentations, the use of colour-highlighted doses on the packaging and no requirement for reconstitution. Recently, an additional filgrastim product has received approval for 72 hours out-of-fridge storage [26] which, while further highlighting the user requirements for additional stability information to support real-life handling and use of these drugs, falls short of providing out-of fridge coverage for routine use in 7-day regimens, as previously described. Additionally, Hospira filgrastim is the only G-CSF currently available that has a low-dose (12 MU) version in a prefilled syringe, thereby minimising wastage for patients who require low doses of filgrastim, and enabling a high degree



**Table 2: Physical and chemical parameters for time-expired Hospira filgrastim following exposure to a range of environmental conditions**

Parameter (mean ± SD)		5°C (control)	Cyclic test*	Cyclic test* followed by 7 days at 25°C		7 days at 25°C		3 days at -20°C
				Exposed to light	Protected from light	Exposed to light	Protected from light	
Hospira filgrastim 30 MU (n = 3)								
pH		4.0 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	4.1 ± 0.1
Number of particles per syringe	≥ 10 µM	162.0 ± 44.9	206.1 ± 19.9	196.1 ± 64.7	153.1 ± 43.1	162.0 ± 19.3	151.0 ± 4.0	355.0 ± 106.1
	≥ 25 µM	0.7 ± 0.6	1.0 ± 0.0	1.0 ± 0.0	0.7 ± 0.6	1.0 ± 0.0	1.0 ± 0.0	3.3 ± 2.6
Hospira filgrastim 48 MU (n = 3)								
pH		4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0
Number of particles per syringe	≥ 10 µM	165.1 ± 1	116.1 ± 8.6	210.0 ± 58.1	219.3 ± 57.3	119.6 ± 4.7	137.7 ± 64.1	315.7 ± 198.0
	≥ 25 µM	1.3 ± 0.6	0.7 ± 0.6	2.3 ± 1.5	2.0 ± 1.0	1.0 ± 0.0	1.7 ± 1.2	1.3 ± 0.6
*Two days at 25°C followed by 2 days at 5°C (repeated three times). Values shown are the mean of three separate batch samples. SD: standard deviation.								

\*Two days at 25°C followed by 2 days at 5°C (repeated three times). Values shown are the mean of three separate batch samples. SD: standard deviation.

**Table 3: Purity parameters for time-expired Hospira filgrastim following exposure to a range of environmental conditions**

Parameter (mean ± SD)	5°C (control)	Cyclic test*	Cyclic test* followed by 7 days at 25°C		7 days at 25°C		3 days at -20°C
			Exposed to light	Protected from light	Exposed to light	Protected from light	
Hospira filgrastim 30 MU (n = 3)							
Filgrastim-related proteins (total, %)	2.5 ± 0.2	2.5 ± 0.2	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.2	2.5 ± 0.2	2.4 ± 0.1
f-met filgrastim and acidic impurities (%)	0.3 ± 0.0	0.4 ± 0.1	0.6 ± 0.1	0.7 ± 0.0	0.3 ± 0.0	0.4 ± 0.0	0.4 ± 0.1
Hospira filgrastim 48 MU (n = 3)							
Filgrastim-related proteins (total, %)	2.0 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	2.0 ± 1.1	2.0 ± 1.1	2.1 ± 1.1
f-met filgrastim and acidic impurities (%)	0.6 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1
*Two days at 25°C followed by 2 days at 5°C (repeated three times). Values shown are the mean of three separate batch samples. SD: standard deviation.							

\*Two days at 25°C followed by 2 days at 5°C (repeated three times). Values shown are the mean of three separate batch samples. SD: standard deviation.

of flexibility in designing treatment regimens. Therefore, among the currently available G-CSFs, Hospira filgrastim provides a range of features that provide direct benefits to pharmacists and patients in a product that continues to be developed with the user in mind. The clinical community looks forward to additional technical innovations and molecular characterisation studies for G-CSFs that may further improve the convenience of these agents for patients.

## Conclusion

In conclusion, current Hospira filgrastim formulations are unaffected by cyclical changes in temperature between the fridge and room temperature (not above 25°C), and are also unaffected by exposure to room temperature (not above 25°C) for seven days or frozen for three days. After exposure to 25°C for

seven days, Hospira filgrastim should not be returned to the fridge. These findings result in benefits of convenience and confidence for physicians, pharmacists and patients concerned with the supply, storage and administration of G-CSF, and highlight how the seemingly technical exercise of exploring the long-term thermal stability of a growth factor therapeutic can lead to tangible benefits for prescribers, pharmacists and patients. Future investigations of protein therapeutics should include stability studies of the type presented here, to ensure that the drugs made available to patients meet the current demands of storage, handling and flexibility.

## Acknowledgements

All of the analyses were conducted by Hospira Zagreb doo Quality Department, with the exception of sterility and bacterial

endotoxins tests, which were conducted by Pliva Hrvatska doo. Data interpretation was provided by the authors. The authors would like to thank Dr Nigel C Eastmond of Eastmond Medcomm Ltd who provided editorial support, which was funded by Hospira Inc.

### Conflict of interest

Mr Bruce Burnett has received financial support as a consultant to Hospira, Teva and Ratiopharm. Ivona Radić Krleža is an employee of Hospira Zagreb doo.

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# Biosimilars in oncology: emerging and future benefits

Professor Matti Aapro, MD; Paul Cornes, MD

The burden placed on healthcare systems by an ageing and expanding population, where cancer is a common disease, is high. The expiration of patents on biopharmaceuticals enables the development and production of similar biological medicinal products, or biosimilars. These agents offer one way of controlling cancer drug expenditure while simultaneously expanding patient access to important medicines.

**T**he burden placed on healthcare systems by an ageing and expanding population, where cancer is a common disease, is high and difficult to manage even in rich countries [1-3]. At the same time, advances in diagnosis and treatment have improved cancer survival rates [4]; however, the financial impact of this progress is considerable, and partially related to increasing expenditure on cancer drugs [5]. For example, the cancer drugs budget in the US rose four-fold in the decade 1998–2008 [6], while in France spending on cancer drugs doubled (from Euros 474 million to Euros 975 million) between 2004 and 2008 [7].

Biological agents account for a substantial number of new cancer treatments, and six of the 10 biggest selling biologicals are used routinely in oncology [8]. This new wave of biologic therapies is effective but expensive. The average cost of a biologic treatment is US\$16,000 per year, although some can cost up to US\$10,000 per month [9]. Oncologists are increasingly concerned by this trend and look to cost savings as the way to preserve patient access to effective treatments [10]. Patents on several biopharmaceuticals used in cancer therapy have recently expired, or are due to expire, in the EU. As a result, pharmaceutical companies are able to develop and produce similar biological medicinal products, or biosimilars [11], with potential benefits for healthcare providers and patients in terms of reducing expenditure on cancer drugs and possibly increasing patient access to treatments.

The difference in price between biopharmaceuticals and biosimilars is likely to be smaller than for originator and generic chemical medicines, since research and development costs for biosimilars are higher [12]. While differences in acquisition price of as much as 80% have been observed between originator and generic chemical medicines, differences between originator biopharmaceuticals and biosimilars are likely to be in the region of 15–30% [12–14]. However, even these comparatively small price differentials would provide substantial cost savings; the European Generic medicines Association estimates that a 20% price reduction on six off-patent biopharmaceuticals would save the EU Euros 1.6 billion annually [15].

Currently in Europe, the only biosimilars available for use in patients with cancer are in the supportive care setting, for the

treatment of chemotherapy-induced anaemia (biosimilar epoetins) and the prevention of chemotherapy-induced neutropenia (biosimilar filgrastims). An analysis of GCSFs (originator filgrastim [Neupogen], biosimilar filgrastim [Zarzio] and peg-filgrastim) across the G5 EU countries showed the biosimilar GCSF to be the most cost-efficient agent for reducing the incidence of febrile neutropenia in cancer patients receiving chemotherapy [16]. The study assessed direct costs (based on the population-weighted average unit dose cost of each agent across the EU G5 countries) to a buyer or payer of purchasing or covering any of these agents for managing one patient during one cycle of chemotherapy under regimens of 1–14 days of standard filgrastim. Use of biosimilar filgrastim resulted in cost savings of Euros 32.70 (1 day) to Euros 457.84 when compared against the originator product. Also, at no point over the 14-day treatment period did pegfilgrastim provide a savings advantage over the biosimilar filgrastim [16].

A similar model has been applied to evaluate the comparative cost-efficiency of different erythropoiesis-stimulating agents (ESAs) for the treatment of chemotherapy-induced anaemia [17]. Direct costs of ESA treatment were calculated for one patient with cancer undergoing chemotherapy (six cycles at 3-week intervals) with ESA initiated at week 4 and continued for 15 weeks. Five scenarios were developed under fixed and weight-based dosing: continuous standard dose for 15 weeks; sustained dose escalation to 1.5 times or double the standard dose at week 7, continued for 12 weeks; and discontinued dose escalation to 1.5 times or double the standard dose at week 7 for a 3-week period, then 9 weeks of standard dose. The ESAs included in the model were epoetin alfa (originator [Eprex] and biosimilar [Binocrit]; once weekly), epoetin beta (NeoRecormon; once weekly), and darbepoetin alfa (Aranesp; once weekly or once every 3 weeks). Under fixed dosing, the average cost of biosimilar epoetin alfa treatment across scenarios was Euros 4,643 (30,000 IU) or Euros 6,178 (40,000 IU); corresponding estimates were Euros 7,168 for originator epo-





etin alfa, Euros 7,389 for epoetin beta, Euros 8,299 for darbepoetin alfa once weekly, and Euros 9,221 for darbepoetin alfa once every 3 weeks. Under weight-based dosing, the average cost of biosimilar epoetin alfa treatment across scenarios was Euros 4,726; corresponding estimates were Euros 5,484 for originator epoetin alfa, Euros 5,652 for epoetin beta, and Euros 8,465 for both darbepoetin alfa once weekly and once every three weeks [17].

An abstract from the recent annual meeting of the American Society of Clinical Oncology described the first validation of the European biosimilar cost-saving model, with the Oncology Center Ettore MS Conti in Italy reporting effective GCSF prophylaxis at lower costs with biosimilar filgrastim [18]. The cost savings made possible through the use of biosimilars in oncology could help to improve supportive care and cancer treatment in a number of ways. For example, use of biosimilar GCSF could allow oncologists and haematologists to more closely follow clinical practice guidelines for reducing the incidence of febrile neutropenia in patients undergoing chemotherapy, by enabling more widespread use of prophylactic treatment. This should result in fewer chemotherapy dose reductions, fewer hospitalisations, and a lower overall cost of treatment [19]. Alternatively, cost savings in the supportive care budget could allow expanded access to potentially life-saving cancer treatments. In one example, it has been calculated that expenditure on epoetins in oncology could be reduced by US\$188 million if all patients (in France, Germany, Italy, Romania, Spain, The Netherlands and UK) were switched to a biosimilar product, and that this saving would support rituximab treatment for around 9,000 extra patients [20].

With patents on several biopharmaceuticals due to expire in Europe by 2014, the number of biosimilar medicines available for use in oncology is expected to increase. Future biosimilar development will focus on medicines such as monoclonal antibodies (mAbs) that offer potentially life-saving or life-extending benefits, with some estimating that biosimilar mAbs will be available around 2015 [21]. EMA has issued a draft guideline on the development of biosimilar mAbs, outlining the non-clinical and clinical requirements [22]. It recommends a risk-based approach to evaluate products on a case-by-case basis, with *in vitro* studies conducted first before a decision is made on the extent of *in vivo* studies required. The guideline also acknowledges the challenges in establishing similar clinical efficacy and safety of a biosimilar and reference mAb in an anticancer setting; these stem from the fact that the preferred endpoints (progression-free, disease-free or overall survival) may be influenced by factors unrelated to differences between the biosimilar and reference mAb (such as tumour burden, performance status and previous treatment). It therefore recognises that surrogate endpoints, such as overall response rate or change in tumour mass, may be acceptable. It is anticipated that final guidance on the development of biosimilar mAbs will be available by mid-2012.

It is clear that the current rate of increase in cancer budgets is unsustainable, even in wealthy countries. Biosimilars, medicines that are similar to biopharmaceuticals that are already approved (and are themselves approved through a well-defined regulatory pathway), offer one way of controlling cancer drug expenditure while simultaneously expanding patient access to important medicines.

### Acknowledgements

Editorial assistance in the development of this manuscript was provided by Tony Reardon of Spirit Medical Communications Ltd, and funded by Sandoz International GmbH.

### Conflict of interest

Both Professor Aapro and Dr Cornes have acted as advisors to, and received speaker fees from, Sandoz.

### For patients

Biosimilar drugs are, as the name suggests, similar versions of already existing treatments. A biosimilar will have similar clinical effectiveness and safety to the already existing treatment, but will typically be less expensive. This is increasingly important in the area of cancer, as the costs of cancer treatment continue to increase. Biosimilars may provide a way of ensuring that patients continue to receive their treatment while at the same time controlling the costs of care.

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# Cardiotoxicity induced by anticancer drugs

Josep Tabernero, MD; Irene Braña, MD

Improvement in the survival of cancer patients has led to antineoplastic drug-induced cardiotoxicity as an emerging concern. Moreover, recent incorporation of targeted therapies has widened the cardiotoxic spectrum, inducing left ventricular dysfunction, acute coronary events or arrhythmias.

## Introduction

Cardiotoxicity was described as an adverse event of antineoplastic agents quite early in the history of modern oncology when the first reports of heart failure induced by anthracyclines were published in the late 1960s [1].

As better efficacy of anticancer therapies is achieved, concerns regarding their cardiotoxicity are rising, particularly given the observation that these chronic adverse events may worsen survivor long-term outcome [2]. In addition, novel mechanisms of cardiotoxicity associated with targeted therapies have been described.

In general, anticancer agents can induce cardiotoxicity not only through left ventricular dysfunction but also ischaemia or rhythm disturbances. Various drugs combine some of these mechanisms, but typically one is predominant [3].

## Heart failure induced by anticancer drugs

Anthracyclines are the archetype of chemotherapeutic agents

inducing left ventricular dysfunction as there is a clear correlation between cumulative dose administered and risk of heart failure (HF). Thirty per cent of patients receiving cumulative doses of doxorubicin exceeding 550 mg/m<sup>2</sup> experience HF, compared to only 5–10% of patients receiving lower doses. Cardiovascular comorbidities have also been shown to enhance the risk of HF, thus additional efforts should be made to identify and treat them both before and during treatment [1]. Moreover, close monitoring of left ventricular function is essential, as early detection and treatment with enalapril and carvedilol has been shown to be beneficial in a small prospective study [4].

Several approaches to improve anthracycline cardiotoxicity are used, such as the development of anthracycline derivatives, including epirubicin or idarubicin, which have a more favourable cardiotoxic profile. Furthermore, liposomal formulations (pegylated and non-pegylated) have been designed to improve drug distribution to the tumour, avoiding healthy tissues and therefore inducing less cardiotoxicity [1].



**Table 1: Risk factors for drug-induced QTc interval prolongation and *torsade des pointes***

Parameter	Risk factor
Gender	Female
Related to drug administration	High drug concentration Rapid rate of IV infusion with a QT-prolonging drug
Electrolyte disturbances	Hypocalcaemia Hypokalaemia Hypomagnesaemia
Previous cardiovascular disease	Myocardial ischaemia Cardiac hypertrophy Congestive heart failure Bradycardia Atrioventricular block Myocarditis
Baseline electrocardiogram alteration	Subclinical long QT-syndrome Baseline QT prolongation
Endocrine disorders	Hyperaldosteronism Hypothyroidism Hyperparathyroidism
Neurological disorders	Stroke Subarachnoid haemorrhage Intracranial trauma
Other diseases	Diabetes Cirrhosis

**Table 2: Drugs inducing prolonged QT interval**

Serotonin agonist/antagonist	Cisapride, ketanserin, zimeldine
Antibiotics	Clarithromycin, erythromycin, sparfloxacin, pentamidine
Antifungal	Ketoconazole, miconazole, itraconazole
Antipsychotics	Phenothiazine, droperidol, haloperidol
Antidepressants	Amitriptyline, clomipramine, desipramine, imipramine
Vasodilators	Bepridil, perhexiline
Antiarrhythmic drugs	IA: procainamide, quinidine, amaline, disopyramide IB: flecaine, propafenone III: amiodarone, sotalol, dofetilide, ibutilide
Other	Methadone

As the cardiotoxic effect of anthracyclines is caused via oxidative stress, the use of antioxidant drugs, such as dexrazoxane, has been evaluated. Although dexrazoxane has been shown to reduce HF incidence in children and adults treated with anthracyclines, there are some concerns regarding a possible increased risk of secondary malignancies and a potential

decrease in anti-tumour efficacy. For this reason, FDA has limited its use to cumulative dosages of doxorubicin exceeding 300 mg/m<sup>2</sup> [5].

The second drug with known associated cardiotoxicity is trastuzumab, an anti-*HER2* monoclonal antibody. Contrary to anthracyclines, trastuzumab-induced cardiotoxicity is reversible and no ultrastructural alteration is observed. These characteristics reflect a different underlying mechanism; there is no irreversible oxidative stress damage, but *HER2* blockage produces a cascade of events that eventually cause ATP depletion in cardiomyocytes [6].

The incidence of trastuzumab-induced cardiotoxicity is about 7% [8], but this rises when trastuzumab is combined with other chemotherapeutic agents, especially with anthracyclines [9]. Additionally, cardiovascular risk factors such as diabetes, dyslipidaemia or obesity, increase left ventricle dysfunction risk [3].

Other drugs associated with an increased risk of left ventricle dysfunction include anti-angiogenic agents. It has been demonstrated that vascular endothelial growth factor (VEGF) signalling in the heart is necessary to adapt to hypertension-related pressure overload. For this reason, its blockage with antiangiogenic agents would favour left ventricle dysfunction, especially since the most relevant toxicity induced by this group of agents is hypertension. It is noteworthy that the incidence of HF with these drugs is lower in comparison to anthracyclines or trastuzumab [6].

## Ischaemia induced by antineoplastic agents

Several anticancer treatments can increase coronary artery disease risk. These include not only chemotherapeutic agents and targeted therapies, but also radiotherapy. Among chemotherapeutic drugs, fluoropyrimidines are the group most strongly associated with coronary events. Angina-like chest pain is the most common presentation but more severe manifestations such as myocardial infarction, arrhythmias, heart failure, cardiogenic shock or sudden death have also been described [9].

It is believed that coronary vasospasm induced by fluoropyrimidines is the main underlying cause; unfortunately, preventive treatment with vasodilators has not been shown to be beneficial [3].

Regarding targeted agents, antiangiogenic drugs are those more closely associated with coronary syndromes. In a pooled analysis of five randomised trials of bevacizumab in combination with chemotherapy, patients in the bevacizumab arm had an increased incidence of arterial thromboembolic events, including acute coronary syndrome (with a 1.5% incidence) [10]. It has been observed that the VEGF pathway is essential for endothelial renewal in response to trauma. Thus, VEGF inhibition with bevacizumab induces endothelial dysfunction and defects in the vascular lining, leaving the subendothelial

collagen exposed [11]. This event activates thrombus formation and, if located in a coronary artery, triggers an acute coronary syndrome.

### Arrhythmogenic risk of anticancer drugs: the role of QTc interval elongation

In the 1990s, several unrelated marketed drugs were withdrawn due to their arrhythmogenic risk. All these drugs could prolong QTc interval and potentially induce *torsade des pointes*, a ventricular arrhythmia that could lead to sudden death [12].

In 2005, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the 'E14 guideline for the clinical evaluation of QT interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs', which stated that the effect on repolarisation of every drug, including anticancer agents, should be evaluated before phase II trials [13].

QTc interval measures total duration of ventricular activation and recovery (depolarisation and repolarisation). Depolarisation and repolarisation are the results of ionic flow through cardiomyocyte membrane. Several drugs can interfere with hERG potassium channels, which are responsible for the rapid component of repolarisation. This interaction ultimately leads to prolongation of repolarisation, which is reflected in the electrocardiogram as a QTc interval prolongation [12].

QTc interval is influenced by heart rate and, for this reason, there are several methods of adjusting the QTc interval according to heart rate [12, 14]. Moreover, several conditions, often observed in cancer patients, see Table 1, might contribute to QTc interval prolongation; thus, careful monitoring and active correction should be made while treating these patients. Furthermore, many drugs can increase the QTc interval prolongation risk, see Table 2, and for this reason, their use in combination with anticancer agents prone to induce QTc interval prolongation should be avoided [14].

In the last two decades, several anticancer drugs have shown a potential effect of inducing QTc interval prolongation. The most relevant of these drugs are arsenic trioxide and histone deacetylase inhibitors. Additionally, all drugs currently in development are monitored according to ICH guidelines to identify an unacceptable arrhythmogenic risk.

### Conclusion

Cardiotoxicity is a major concern when treating cancer patients. The incorporation of targeted therapies which are able to induce cardiotoxicity through ventricular dysfunction, ischaemia or rhythm disturbances has widened the cardiotoxic effect of anticancer drugs. Better knowledge concerning potential cardiac side effects of antineoplastic drugs and the identification of patients at higher risk is a key strategy to reduce cardiotoxicity of these agents.

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# New treatment options for bone metastases in metastatic prostate cancer

Approximately 90% of all patients with castration-refractory prostate cancer develop bone metastases in their disease progression. In the past, bone metastases have been treated with surgical interventions, radiotherapy and bisphosphonates. Recently an alpha-ray applied intravenously has been introduced which is able to reduce symptoms and significantly improve overall survival.

Approximately 90% of all patients with metastatic castration-refractory prostate cancer have radiologically evidenced bone metastases [1]. The consequences are particularly, pathologic fractures, pains and spinal cord compressions with paralysis extending to paraplegia [2].

Furthermore, bone metastases are often the reason for physical handicaps, a limited quality of life and increased expenses [3].

In the past bisphosphonates, surgical interventions and conventional radiotherapeutic options have been used for the treatment of bone metastases, as well as supportive morphine derivatives for pain reduction.

In 70% of all patients, pain reduction can be achieved and in 50% complete pain relief by using the conventional radiotherapy, whereby the onset of effect is to be expected in the second week. The effect mechanism consists of a tumour decrease with consecutive pressure relief at the periosteum with nerve root decompression. Moreover it is assumed that by means of percutaneous radiotherapy a reduction of pain mediator release is obtained as well as a change of the ambience around the nociceptors.



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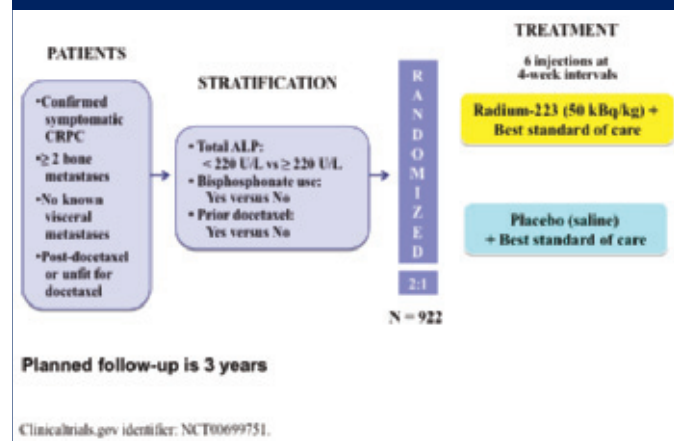
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At the 2012 ASCO Genitourinary Cancers Symposium, radium-223 chloride was introduced under the name 'Alpharadin'. Results of a phase-III-trial (ALSYMPCA) were presented of patients with bone metastases in metastatic prostate cancer [4]. Radium-223 is located in the periodic system of elements in the vicinity of calcium which is required for the bone constitution. Radium-223 is similar to the structure of calcium, however it is an unstable radionuclide and emits alpha-rays. Alpha-rays are characterized by the fact that they have a short penetration depth of 2–10 cell diameters, so that almost no problems are to be expected regarding radiation protection.

Alpha-rays have a high relative, biologic efficacy which is 10–20x higher than conventional gamma-rays or X-rays. The design of the randomized trial, see Figure 1, has been established as follows: 922 patients have been included.

All patients suffered from a symptomatic castration-refractory prostate cancer with two or more bone metastases without visceral metastases. Chemotherapy with taxotere was allowed. The stratification occurred according to the value of the alkaline phosphatase, after the use of bisphosphonates and after prior chemotherapy.

**Figure 1: ALSYMPCA (Alpharadin in SYMptomatic Prostate Cancer) Phase III study design**



**Figure 2: ALSYMPCA overall survival**

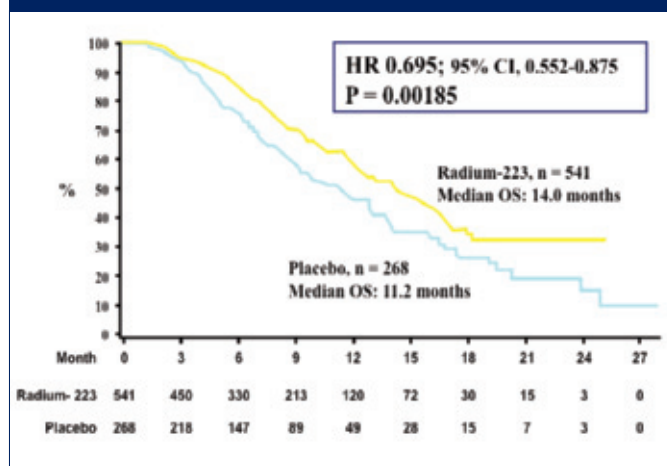
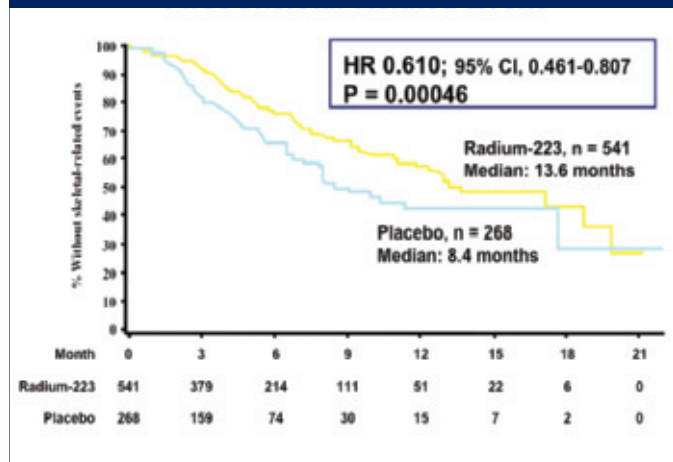




Figure 3: ALSYMPCA time to first skeletal-related event



In total in the verum group six injections in a 4-week interval were given whereby a single activity of 50 kBq/kg was applied. The control group was treated with saline as well as symptomatic therapy. The primary endpoint of the study was the overall survival and the result was a significantly prolonged survival of 14 months in the Alpharadin-group versus 11.2 months in the placebo-group, see Figure 2.

Regarding the appearance of skeletal-related events, a significant advantage in favour of Alpharadin has been found, see Figure 3. In 33% of all patients a total normalization of the alkaline phosphatase has been found whereas this fact has been evidenced only in 1% of the patients in the placebo group ( $p \leq 0.001$ ). The substance is very well tolerated, the anaemia rate of grade III or IV was identical with the placebo group, Concerning thrombocytopenia, we have evaluated a 4% increased side effects in comparison to the placebo group. Regarding non-haematologic side effects such as diarrhoea, nausea and vomiting; there was no difference to the placebo group, see Table 4.

In summary, therefore, it can be stated as follows: Radium-223 significantly prolongs the survival at hazard ratio of 0.695%. Radium-223 significantly prolongs the time to the appearance of the first skeletal-related event, such as fractures ( $p = 0.00046$ ; hazard ratio 0.610). Radium-223 seems to be significantly more effective than the external radiation therapy, and is very well tolerated.

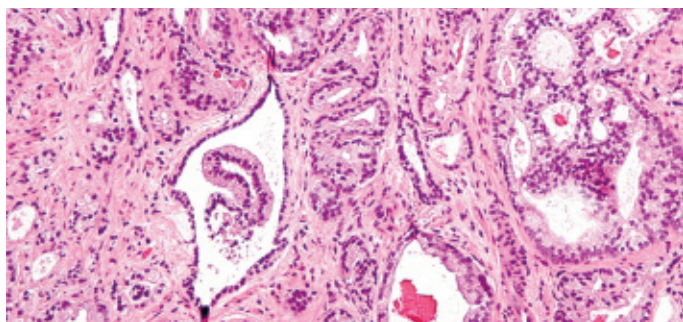


Table 4: ALSYMPCA adverse events of interest

	All Grades		Grades 3 or 4	
	Radium-223 (n = 509) n (%)	Placebo (n = 253) n (%)	Radium-223 (n = 509) n (%)	Placebo (n = 253) n (%)
Haematologic				
Anaemia	136 (27)	69 (27)	54 (11)	29 (12)
Neutropenia	20 (4)	2 (1)	9 (2)	2 (1)
Thrombocytopenia	42 (8)	14 (6)	22 (4)	4 (2)
Non-Haematologic				
Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
Diarrhea	112 (22)	34 (13)	6 (1)	3 (1)
Nausea	174 (34)	80 (32)	8 (2)	4 (2)
Vomiting	88 (17)	32 (13)	10 (2)	6 (2)
Constipation	89 (18)	46 (18)	6 (1)	2 (1)

It is anticipated that Alpharadin will become the new standard in the treatment of skeletal-related metastatic prostate cancer after its approval which is expected in a short time.

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# ASCO 2012: rising cost of cancer care and chemotherapy drug shortages

Professor Dr med Günther J Wiedemann, MD, PhD; Professor Dr med Wolfgang Wagner, MD, PhD

At the Annual Meeting of the American Society of Clinical Oncology (ASCO) 2012 in Chicago, USA, professional discussions addressed the most recent study results in oncology. But there was yet another focus: health issues that need to be solved politically.

**A**lthough costs associated with prevention, therapy, and surveillance in patients with cancer after completion of treatment are a relatively small fraction of the total cost, the increasing incidence of cancer in the population and greater expense associated with new therapies pose a direct challenge to our healthcare systems. In this situation, the overuse of interventions and treatments for which there is no evidence to support use, can no longer be tolerated. The assumption that follows is that curtailment of these practices would be associated with enhancement in the quality of health care, as well as with reduced cost. The Foundation of the American Board of Internal Medicine embraced this concept and developed 'choosing wisely', an educational campaign that is motivated by the importance of conversations between physicians and their patients about the evidence underlying treatment plans. It is anticipated that the consequence of such conversations will be fewer interventions, leading to improved patient care and to the notable side benefit of lower cost.

## The top five list: practices or interventions that are costly, widely used, and not supported by high-level clinical evidence

American Society of Clinical Oncology (ASCO) joined this initiative. The task was to identify five commonly used practices, i.e. granulocyte colony-stimulating factors or imaging modalities, in each specialty for which there is no evidence to support use. It might sound cynical to cancer patients, but unsurprisingly, there was an abundance of corresponding suggestions [1].

## The oncology drug shortage crisis

First noted in December 2010 in the US, the shortages of cytarabine, doxorubicin, cisplatin, paclitaxel, etoposide, mechlorethamine, methotrexate, daunorubicin, cytarabine, fluoruracil and folinic acid and the impact on patients with cancer has been brought into focus through work performed by ASCO this year [2]. Consequently, FDA announced a series of steps to increase the supply of critically needed cancer drugs and build on President Obama's executive order to help prevent future drug shortages. It is believed that the unifying mechanisms behind the drug shortages can be traced to simple economics. Manufacturers have little incentive to produce drugs with low profit margins and often shift their resources to drugs for which higher profit margins can be anticipated. For the past two years, an unprecedented number of drug shortages have plagued hospitals, clinics, and physician practices across Europe and the US, threatening all types of patient care [3, 4].

The shortages are not unique to chemotherapeutic agents but occur across a broad range of medicines. Chemotherapy drug shortages are generally more critical because of the lack of equivalent alternatives for most agents. We are equally concerned about other types of drugs in shortage. Anaesthesia drugs, such as benzodiazepines, propofol, and fentanyl injections have also been in short supply. Drug shortages remain a serious, complex problem and ASCO remains extremely concerned about all current and potential shortages.

## Studies reporting progress in patient-centered care

**Mapisal** (150 g; 3 x daily; Medac, Wedel, Germany), a topically applied ointment with high radical protection factor as a prevention strategy against the hand-foot syndrome, see Figure 1, was found to be active in female patients with ovarian carcinoma during and after the treatment with pegylated doxorubicin monotherapy at a dose of 40 mg/m<sup>2</sup> every 28 days [5]. The protective capacity of Mapisal versus urea cream is currently investigated in a phase III clinical trial in patients treated with capecitabine, a cancer therapy which is often followed by a hand-foot syndrome.

**Duloxetine** (one 30 mg capsule daily for one week; Cymbalta; Merck, Darmstadt, Germany), a serotonin-norepinephrine reuptake inhibitor anti-depressant is the first effective treatment for chemotherapy-induced peripheral neuropathy (painful peripheral neuropathy with numbness and tingling in the hands and feet affects 20–30% of cancer patients treated with taxanes and platinum-based chemotherapy; phase III double blind CALGB trial) [6].

**Paclitaxel** (weekly 90 mg/m<sup>2</sup>) is significantly better (more effective and less toxic) than the more costly newer drugs Abraxane (nanoparticle albumin bound paclitaxel; 150 mg/m<sup>2</sup>) and Ixempra (ixabepilone; 16 mg/m<sup>2</sup>) as first-line therapy for locally recurrent or metastatic breast cancer—phase-III-randomised trial, 799 patients [7].

## Major trials resolving important debates, leading to new standards of cancer care

**Bendamustine** (Ribomustin 90 mg/m<sup>2</sup>, day 1, 2) combined with Rituximab (375 mg/m<sup>2</sup> day 1) is less toxic (no alopecia, less haematotoxicity, G-CSF use, infections, and neuropathy) and more effective (significantly improved performance status, and higher complete response rates) than CHOP (Cyclophosphamide 750 mg/m<sup>2</sup> day 1, Doxorubicin 50 mg/m<sup>2</sup> day 1, Vincristine 1.4 mg/m<sup>2</sup> day1, Prednisone 100 mg days 1–5) combined with Rituximab (375 mg/m<sup>2</sup> day 1). Long-term results from a multicentre phase III

Figure 1: Hand-foot syndrome\*



\*palmar-plantar-erythrodysesthesia—following treatment with pegylated liposomal doxorubicin or with capecitabine [11].

study showed a more than doubled progression-free survival, to nearly six years, compared with standard R-CHOP therapy among patients with indolent and mantle cell lymphomas [8].

**Intermittent androgen deprivation** is less effective than continuous androgen deprivation in men with hormone sensitive metastatic prostate cancer with minimal disease spread. There was a two-year difference in median survival among these men, favouring men who received continuous therapy. This National Cancer Institute-sponsored international intergroup phase III study was designed to see if intermittent hormonal therapy achieved survival comparable with continuous therapy [9]. The trial included more than 1,500 men with hormone-sensitive metastatic prostate cancer whose PSA fell to 4 ng/mL or less after seven months of continuous hormonal therapy. After a median follow-up of 9.2 years, median overall survival in men with minimal disease spread (no spread beyond the spine, pelvis, and lymph nodes) was 7.1 years for those who received continuous therapy versus 5.2 years for those who received intermittent therapy. Among men with more extensive disease spread, median overall survival was similar in both arms—4.4 years for the continuous therapy versus five years for the intermittent group.

**Adjuvant Procarbazine, CCNU, Vincristine (PCV; 6 cycles)** after standard radiation (59.4 Gy) delayed tumour growth and extended the lives of patients with anaplastic oligodendroglial tumours—a form of brain cancer. A sub-analysis of the study showed the survival benefit of combination chemotherapy—radiation treatment might be limited to patients whose tumours contained specific deletions of genetic material in chromosomes 1 and 19 (1p/19q co-deletions). This long-term follow-up results of a phase III EORTC trial [10] give evidence that adjuvant PCV increases survival in anaplastic oligodendroglioma—progression-free survival was 24.3 months in the radiation/PCV group and 13.2 months in the radiation only group; overall survival was 42.3 months in the radiation/PCV group and 30.6 in the radiation only group, especially in patients with 1p/19q co-deleted tumours.

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