

## Editorial

Let this special light shine 2

## Cover Story Stability of Anticancer Drugs in Clinical Practice

The practical stability of anticancer drugs: SFPO and ESOP recommendations 4

SFPO and ESOP recommendations for the practical stability of anticancer drugs 7

## Oncology Pharmacy Practice

Improving chemotherapy capacity by switching from IV to oral vinorelbine 14

## Feature - ESOP/NZW 2010 Congress Report

Survey of weekend work by ESOP members 19

Iron and erythropoiesis-stimulating agents in anaemia 20

European use of devices supporting safe handling of cytotoxic drugs 22

## Industry Science

Physical and chemical stability of cisplatin infusions in PVC containers 11

Physical and chemical stability of Taxotere® 1-vial 20 mg/1 mL infusion solution following refrigerated storage 24

## Special Report

Current situation of cytotoxics preparation in Europe – an ESOP online survey 27

## Update

Chemotherapy in the elderly: the critical factors 28

## Guideline

Chemotherapy-induced nausea and vomiting: what are the best treatments 30

## Comment

Motivating cancer patients by personality type 31

ESOP News 3

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# Let this special light shine

**T**he season's greetings seem to fall together with thoughts about the future. To where should the lighthouse of pharmacy show the way?

Since the days when Emperor Frederic divided one group of official health workers into two groups, physicians and pharmacists, pharmacists' professional image of themselves has yet to be established.

Many of the physicians today continue to practise (or prescribe) in a traditional manner, where pharmacists are finding their way to adapt to new challenges.

Being the second part of the whole, having lost the closeness to the patient, having organised the productions of creams and solutions into an industrial standard, hospital pharmacists are starting to reinvent themselves.

In the special field of oncology, which has been supported step by step by pharmaceutical science for the last 30 years, pharmacists have the chance to go back in time through this process of self-evaluation to their misunderstood roots. Here also we have started the transfer of knowledge far from direct contact with patients. We have shown responsibility in educating ourselves in aseptic work and stability. The first parts of the Quality Standard for Oncology Service (QuapoS) cover these basic topics in total.

In this issue we highlight some of these points when we proudly present the latest thoughts in practical stability of anticancer drugs: the SFPO and ESOP recommendations. Ready to use in Europe, they gather together practical work done by pharmacists throughout Europe and in many cases recommend improved storage times. This major report is



Klaus Meier  
Editor-in-Chief



accompanied by an article on the use of devices supporting safe handling of cytotoxic drugs and an assessment of weekend work done by ESOP members.

On the other hand the achievement of pharmacy cannot be restricted to practice alone. The nature of our work, being close to the patient and his illness, is the cause of our efforts and professionalism. That's why we are making great efforts to improve collaboration with the whole healthcare team and to present the multi professionalism to patients.

We are making progress in knowing more about chemotherapy in the elderly, by comprehending their emotional and treatment needs and discerning the critical factors. In general we are establishing guidelines for the most important side effects by implementing supportive care to provide patients with the best treatment. We are publishing guidelines about chemotherapy-induced nausea and vomiting in this issue too.

These subjects, which are occurring to pharmacists in hospitals who see their work as patient-oriented, are rapidly becoming relevant to those pharmacists who are working in the community. The need to support patients in ways other than reflecting about drug interactions, for example, getting involved in adherence, is a great challenge for forward-looking pharmacists.

The good use of oral cytotoxic drugs is becoming one of the mainstream areas in which pharmacy can justify its right to exist. All of these advances also bring light to those who feel lost in a welter of regulations that have to be followed accordingly, without advancing medical or scientific knowledge or offering patient benefits.

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### **Ninth National Medical Oncology Conference: the latest in medical oncology in Romania**

The National Symposium on Medical Oncology in Romania (ESMO-SNOMR) was held in the beautiful ski resort of Poiana Brasov, 23–26 September 2010. The conference updated participants on recent topics such as the combination of positron emission tomography with computerised tomography in the visualisation of tumours, new drugs in oncology, supportive treatment and reports on clinical trials.

ESOP was represented with a lecture on safety in cytotoxic drug handling given by Professor Per Hartvig and Ms Eva Honoré from Copenhagen, Denmark. They concluded that effects of cytotoxic drugs on personnel are seldom reported. Several studies have shown a moderately increased prevalence of stillbirths, congenital malformations and miscarriages in nurses handling cytotoxic drugs compared to controls. A meta-analysis concluded that the rate of stillbirths and congenital malformations was not significantly increased whereas the risk of miscarriages was increased with an odds ratio of 1.46 (CI: 1.11–1.92). Menstrual cycle dysfunction has shown a moderate increase in females over the age of 30. It has not been possible to detect cytotoxic-induced cancer in handling personnel.

It is important to communicate that adequate protection is essential during preparation and that the risk to personnel is fairly small. High safety awareness is mandatory as well as high quality. Good Manufacturing Practice must be followed where appropriate. This requires an organisation knowledgeable in risk assessment and handling, suitably educated personnel, facilities for minimum exposure during preparation, protective equipment, high quality standards and quality control including efficient and complete documentation and a documented awareness of incidents and threats to safety and production quality. The necessary procedures are found in QuapoS 4 - Quality Standard for the Oncology Pharmacy Service with Commentary, ESOP 2009.

The present situation in Romania is that the nurses mostly prepare the cytotoxic drugs on the ward without any particular safety clothing or procedures, and there was great interest in the ESOP presentation.

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# Improving chemotherapy capacity by switching from IV to oral vinorelbine

Oral vinorelbine reduced the time spent by patients and pharmacists in chemotherapy delivery but care pathways differed across the EU facilities studied. Possible reasons include differing organisation and competency frameworks.

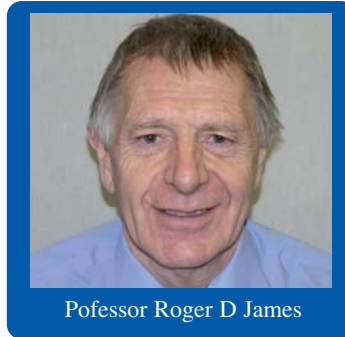
## Introduction

Chemotherapy facilities deliver treatments using a complex interaction between nurses, pharmacists and doctors. There is a wide consensus that one should define optimal delivery by qualitative criteria (safety, patient-centred care) as well as quantitative criteria (efficiency and financial balance). However, no international guidelines define the optimal service model for achieving safety and efficiency. Over the last ten years across the EU, there have been rapid increases in demand for chemotherapy for advanced non-small cell lung cancer (NSCLC) and metastatic breast cancer (MBC) and this trend is likely to continue [1]. Increased utilisation of chemotherapy is associated with pressures on the resources needed for service delivery [2-6].

The number of orally active agents available, particularly the targeted therapies, is also likely to increase substantially for the foreseeable future [4]. The global market of biological therapies for cancer, many of which are oral, is projected to rise from US\$37.9 billion in 2009 to US\$53.7 billion in 2014, a five-year compound annual growth rate of 7.2% [7]. Oral products have been shown to improve patient-centred care by allowing treatment at home, avoiding long waits and journeys and the need for central lines. Oral chemotherapy can also improve productivity and profitability in chemotherapy facilities [8-10].

Vinorelbine (Navelbine, Pierre Fabre Limited) is a standard treatment for advanced NSCLC and MBC. Its oral formulation (Navelbine Oral, Pierre Fabre Médicament) is bioequivalent, clinically equivalent and similarly well tolerated. It was recently introduced as a line extension of IV vinorelbine. Vinorelbine is one of four modern agents recommended by NICE for the treatment of advanced NSCLC, either in combination with cisplatin or carboplatin, or as single agent. Vinorelbine is the only NICE-approved chemotherapy agent available in both an oral and IV formulation. Oral vinorelbine is bioequivalent with the IV formulation so any IV dose can be substituted with oral vinorelbine [11].

Taylor et al. showed that patients treated with oral vinorelbine spent 1 h 30 min less in hospital and required 33% less pharmacy time than patients treated with IV vinorelbine [12]. Le Lay et al. have shown improvements in productivity and health



Professor Roger D James

resource utilisation due to oral vinorelbine compared with IV products [13]. The *care pathway* for chemotherapy service delivery is complex, requiring expertise from differing professional groups, including doctors, pharmacists and nurses.

## Objectives

The objective of Tamino (time and motion international study with Navelbine oral) was to explore across the EU whether switching from

IV to oral vinorelbine as a single agent for patients treated at the hospital for advanced NSCLC or MBC would result in a similar reduction of time for patients, doctors and pharmacists.

## Study design

A time and motion audit was carried out on chemotherapy pathways for patients receiving vinorelbine as part of their chemotherapy treatment, either in IV or oral form. The audit was carried out in eight chemotherapy facilities with diverse patient care pathways situated in four EU countries: Denmark (2 centres), Germany (2 centres), Italy (3 centres) and Spain (1 centre), see Table 1.

Table 1: Study design

Variable	Materials
Countries (Facilities)	Italy (3) Germany (2) Denmark (2) Spain (1)
Measurements	Process times: <ul style="list-style-type: none"> <li>• blood test</li> <li>• consultation/prescription</li> <li>• pharmacy preparation/dispensing</li> <li>• post-treatment observation</li> </ul> Waiting times: <ul style="list-style-type: none"> <li>• between processes</li> </ul>
Patients	Number: 121 (average of 15 patients [range 8-20] at each centre) Diagnosis: <ul style="list-style-type: none"> <li>• Non Small Cell Lung Cancer (NSCLC): 81 (67%)</li> <li>• Advanced Breast Cancer (ABC): 40 (33%)</li> </ul> Measurements performed: <ul style="list-style-type: none"> <li>• Oral vinorelbine: 72 (60%)</li> <li>• IV vinorelbine: 49 (40%)</li> </ul>
Calculations	Average and standard deviation for each process-time

### Inclusion and exclusion criteria

To be included, patients had to be eligible for vinorelbine-based chemotherapy in NSCLC or MBC, with Karnofsky performance status 80% or above. Patients for oral vinorelbine were required to have adequate gastrointestinal absorption. Patients were excluded if they were taking part in another investigation protocol or receiving treatment at home.

### Regimens

Patients were either receiving single agent vinorelbine (mono-chemotherapy) or vinorelbine in combination with other agents (combination chemotherapy). However, for consistency, in those receiving combination chemotherapy, measurements were restricted to those cycles when only vinorelbine (IV or oral) was administered. For example, in a patient receiving oral vinorelbine on days 1 and 8 in combination with cisplatin or trastuzumab, only the day 8 event (when vinorelbine was administered as a single agent) was measured.

### Pathway mapping and measurements

For each patient included, only one administration of chemotherapy was recorded. An observer followed the care pathway of the patient and recorded on a time sheet the time of beginning and end of four distinct processes: the blood test, the consultation and prescription, the pharmacy preparation and dispensing, post-treatment observation. In addition the waiting times between processes were measured and interfering events (telephone calls, questions from other patients or from colleagues) were also recorded and taken into account when appropriate.

From the times measured, the four following durations were to be calculated: overall time spent by the patient at the hospital, consultation, preparation and dispensing, monitoring after administration.

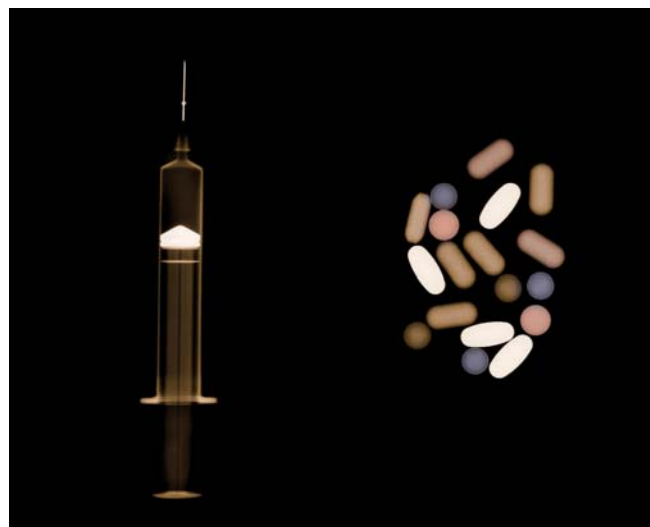
### Informed consent

Local Research Ethics Committees have been approached for advice on the need for informed consent for a related study. It was felt that this was an audit of process times with no impact on the treatment prescribed and no patient interviews, and that no informed consent was required.

### Statistical Analysis

The statistical analysis was performed by *Institut de Recherche Pierre Fabre*. Data were analysed using the SAS system software version 8.2 for Windows. Data collected in this study were mainly endpoints expressed in hours and minutes. Continuous data were summarised with the following items: frequency, median, range, mean and standard deviation if relevant. Categorical data were presented in contingency tables with frequencies and percentages of each modalities including missing data modality. Summary tables and listings were provided by drug (oral or IV vinorelbine) and overall.

Overall time spent by the patient at the hospital was calculated from 'patient arrives at the hospital' to 'patient leaves the

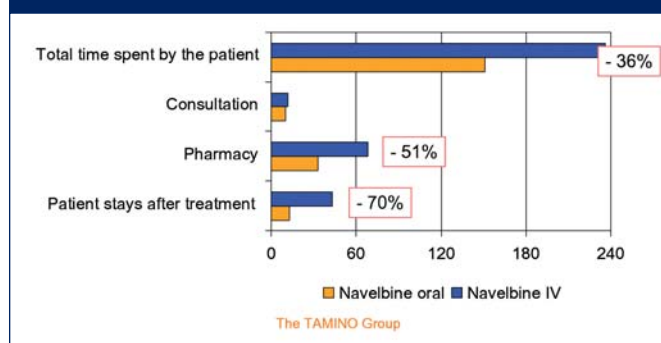


hospital'. Duration of consultation was the time from 'consultation starts' to 'consultation ends'. Duration of preparation and dispensing was the time from 'prescription arrives at the pharmacy' to 'treatment arrives at the clinic'. Duration of monitoring after administration was calculated from 'infusion ends' or 'capsules taken' to 'patient leaves the hospital'.

### Results

A total of 121 patients were included with an average of 15 patients at each centre (range 8–20). Diagnoses were: NSCLC 81 (67%), MBC 40 (33%). Vinorelbine was given by mouth in 72 measurements (60%) and by IV infusion in 49 measurements (40%). Global results showed that overall time spent by the patient, preparation and dispensing, and monitoring after administration were shorter when vinorelbine was given by mouth; only consultation showed no difference, see Table 1 and Figure 1. With regard to overall time in the facility, patients treated with oral vinorelbine spent on average 2 h 31 min relative to 3 h 56 min with IV vinorelbine, a 36% reduction, see Figure 2. The duration of consultation and prescribing by the oncologist was similar for oral vinorelbine and IV vinorelbine; 10 min relative to 12 min respectively, see Figure 3. The time for preparation and dispensing was 33 min for oral vinorelbine relative to 1 h 8 min for IV vinorelbine, a 51% reduction, see Figure 4. The time for observation after admin-

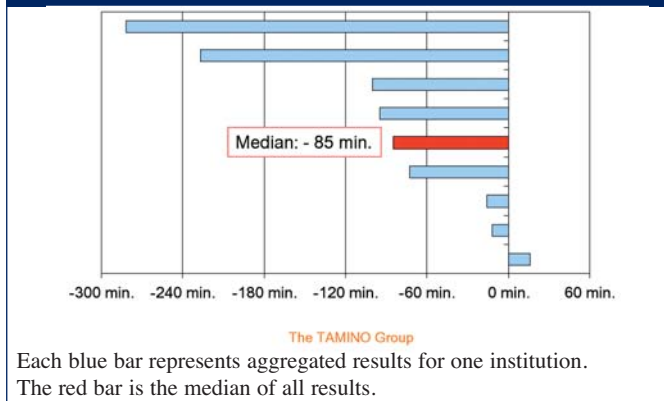
Figure 1: Global result - Navelbine oral versus Navelbine IV



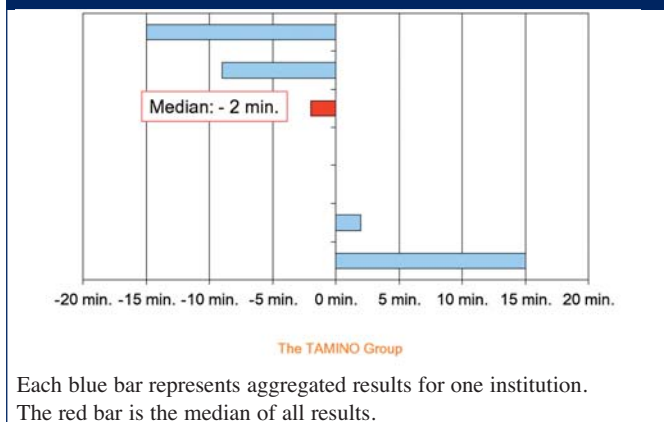


istration was 13 min for oral vinorelbine relative to 43 min for IV vinorelbine, a 70% reduction, see Figure 5. Results were heterogeneous across the eight facilities regarding comparative process times between oral and IV vinorelbine. Comparing the overall time spent by the patients at the hospital resulted in a clear advantage for oral vinorelbine in five facilities, a modest advantage for oral vinorelbine in two, and a modest advantage for IV vinorelbine in one, see Figure 2. Comparing the time for preparing and dispensing resulted in a clear advantage for oral vinorelbine in six centres and a slight advantage for IV vinorelbine in two, see Figure 4.

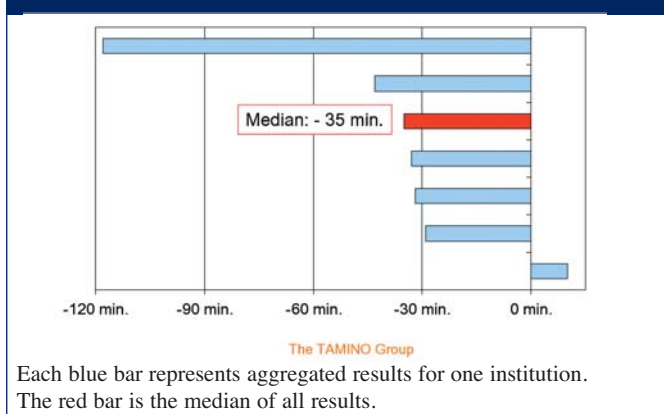
**Figure 2: Overall time spent in the hospital - in favour of oral**



**Figure 3: Consultation/prescription time - in favour of oral**



**Figure 4: Preparation and dispensing - in favour of oral**



**Discussion**

There are commonalities and differences across the EU in the way a single chemotherapy agent is delivered. This audit demonstrates that, summing data from the eight facilities studied, it takes less time to prepare and administer oral vinorelbine than equivalent IV chemotherapy and overall, patients spend less time in the facility. Patient-centred care is improved by reductions in waiting time. However, overall there was no difference in consultation/prescription times between oral vinorelbine and IV vinorelbine. The main savings were in the preparation and dispensing time and in the time taken in observation after treatment. This audit did not measure the administration time of IV vinorelbine, but published data shows a clear reduction in favour of administration (dispensing) of oral vinorelbine relative to IV vinorelbine [12].

However, the data from this study were heterogeneous; there were up to three-fold ranges between facilities in times for the same process and in one facility both preparation/dispensing time and observation time after treatment were shorter for IV vinorelbine than for oral vinorelbine. Further research is required to understand the reasons for differing care pathways in chemotherapy facilities across the EU. Possible variables include the type of facility (hospital bed, ambulatory centre or office), the way how pathways are designed for patients receiving oral or IV treatment, the skill mix of different professionals (nurses, pharmacists, oncologists) and the machinery for re-imburement of the facility.

This audit included only single agent treatment and did not consider the platinum doublets that are commonly used in NSCLC. It could be argued that if a patient is attending for administration of IV platinum on day one, there is little advantage in switching the other drug from IV to oral. However, an independent study has identified time savings on day one as well as on day eight, particularly for nurses and patients [14].

Most patients prefer oral to IV chemotherapy administration [15-18]. In a questionnaire completed by 59 women with breast cancer, 58% answered that “oral chemotherapy would be advantageous”, “would allow them to feel less sick”, and about 40% that “oral chemotherapy would require less effort than IV treatment.” [19]. In another study, 61 patients with NSCLC treated with vinorelbine plus carboplatin were randomised into two arms. For cycles 1 and 2, patients in one arm received vinorelbine by mouth and patients in the other arm received it by IV infusion. All underwent a cross-over for cycles 3 and 4. Finally, they were asked to choose oral or IV vinorelbine for the two subsequent administrations: 74% preferred oral vinorelbine, even combined to IV carboplatin, versus 24% for IV vinorelbine. The choice was independent of whether the patient experienced initially IV or oral vinorelbine and also independent of sex or age [20].

The preparation of IV chemotherapy requires intense labour, time-consuming aseptic preparation by trained pharmacy tech-

nicians in an isolator cabinet. Some facilities rely on off-site aseptic compounders to prepare chemotherapy and switching from IV to oral may reduce the need for off-site compounding, enabling local pharmacies to regain control of preparation and dispensing and encouraging more flexible working practices.

Some service providers have encountered financial incentives that discourage the switch from IV to bioequivalent oral preparations. Acquisition costs may be higher for oral than for the IV equivalent. Reimbursement and tariffs may vary from state to state within the EU [21]. In the EU, as in the US, the dispensing of oral agents from ‘high street pharmacies’ rather than within the chemotherapy facility may result in a loss of payment to the facility relative to the IV equivalent.

With adequate training and governance frameworks, some oral drugs such as vinorelbine may be dispensed from an outpatient pharmacy satellite or in outreach clinics at units, reducing patient waiting and journey times. However, the governance of oral chemotherapy and of nurse-led services is critically important in making service change safe [22]. A *UK National Patient Safety Agency Rapid Response Report* in January 2008 on the administration of oral chemotherapy concluded ‘Doctors, nurses, pharmacists and their staff must be made aware that the prescribing, dispensing and administering of oral anticancer medicines should be carried out and monitored to the same standard as injected therapy.’ [23]. The governance for oral chemotherapy, particularly for a nurse-led service, requires an agreed protocol base as well as a knowledge and skills framework. In UK the legislative background is set out by the Department of Health and professional health organisations [24-29]. The National Cancer Peer Review (NCPR) is the national quality assurance programme for NHS cancer services. NCPR publishes assessments of local services against chemotherapy specific measures [29].

A UK prospective audit confirmed that clinical outcomes following the switch from IV to oral were satisfactory [30]. Costly workforce and capital expansions should be predicated by improvements in productivity, including service re-design [31]. Oral chemotherapy facilitates patient-centred care closer

to the patient’s home [32-34]. Workforce developments include competency frameworks to enable trained nursing.

**Conclusion**

Care pathways differed across the EU chemotherapy facilities studied, but overall, oral vinorelbine reduced the time spent by patients and pharmacists in chemotherapy service delivery relative to IV vinorelbine. For patients there was a 36% reduction in attendance time, for pharmacists a 51% reduction for preparation and dispensing time, for nurses delivering chemotherapy a 70% reduction for post-treatment monitoring (a previous study showed a 60% reduction in nurse delivery time). However, in this study, for doctors there was no change in the duration of the oncology consultation and prescription. The methodology used in this study may be applicable to the introduction of other oral products. Pathway mapping and timing can be a significant driver for chemotherapy service reconfiguration. Further research is required to understand the reasons for differing care pathways in chemotherapy facilities across the EU.

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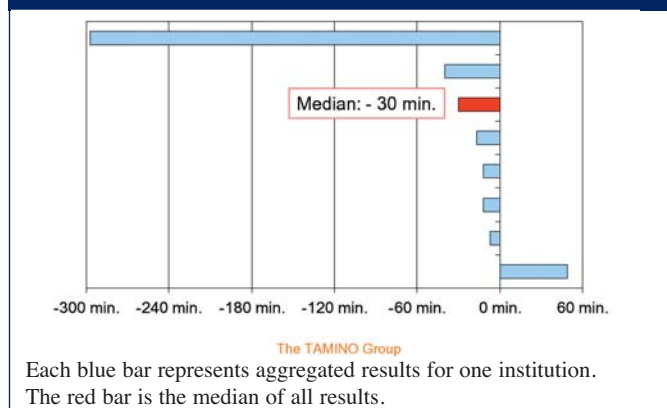
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**Figure 5: Observation after administration - in favour of oral**



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# Survey of weekend work by ESOP members

Many oncology pharmacists avoid working at weekends, although emergency cover is also common. How long will this happy position last?

**T**he North Estonian Medical Centre in Tallinn, Estonia, which has approximately 900 hospital beds and provides a wide range of medical care, is one of the biggest hospitals in Estonia and one of the two hospitals that provides oncologic and haematological treatment. The other hospital is Tartu University Hospital. In March 2008, our hospital pharmacy started a centralised preparation unit for cytotoxics. We were the first to provide this service: the equipment was unique in Estonia, in fact, in the whole of the Baltic region at the time. We had two laminar air-flow cabinets and an online application called Cato (computer aided therapy for oncology). The doctor uses this application to request and calculate the treatment, pharmacists prepare the individual doses and nurses indicate when they have administered it. Last year we made approximately 18,500 preparations. These are for solid tumours only; chemotherapy for patients with haematological conditions is still made on the haematology ward by the nurses.



Kristjan Kongi

We started working five days a week from Monday to Friday. Preparations for the weekend were sent to the wards where they were made by the nurses during the weekends. After some months the nurses started protesting about making the cytotoxic preparations at the weekends. This raised the question of how to do the work over the weekends. Two main questions were brought up: who should work and when?

After a discussion we started preparing drugs in advance for patients who stayed in the hospital over the weekends but a remaining problem was making about 10 new preparations maximum for the two or three new patients who were registered on Saturdays. We started working at the weekends because it was impossible to prepare the drugs in advance for those few patients. The doctors do not have the results of their tests before the weekend.

To find out the situation of hospital pharmacies working elsewhere in Europe we carried out an inquiry among ESOP members. The inquiry involved questions about workflow and workload during the weekends, and whether our colleagues work during the weekends at all.

Individual hospitals from 12 countries answered the questionnaire. In general the answers could be divided into three major groups as follows:

1. Pharmacies work only if there is an emergency.
2. Pharmacies work during weekends (only on Saturdays or possibly the entire weekend).
3. Pharmacies do not work at weekends and preparations are made in advance or are made on the wards by the nurses during the weekends.

3. Pharmacies do not work at weekends and preparations are made in advance or are made on the wards by the nurses during the weekends.

For example in Heidelberg University Hospital, Germany, chemotherapy is prepared regularly on Saturday and Sunday mornings because of the very limited stability of a few drugs. This is also the situation at TweeSteden Ziekenhuis in The Netherlands.

In contrast, in Cancer Centre Henri Becquerel, France, if unstable drugs have to be prepared, kits are given out to nurses who prepare infusions in the wards. These kits contain Securmix devices, gloves and a gown. The kits include a prescription and instructions about the procedure for each infusion. The situation is similar in Ljubljana Institute of Oncology, Slovenia, where unstable drugs are given out to the wards and nurses prepare the treatment.

In many hospitals the pharmacies are closed during the weekends while in some hospitals, pharmacists are available for emergency calls/preparations if necessary. This is the case in Apotek Lanspital Hringbraut, Iceland, Instituto Oncologico San Sebastian, Spain, and Pharmacie Interhospitalière de la Côte, Switzerland.

After considering the answers, we presented an overview to the Head of our oncology ward. As there are only up to 10 preparations per weekend for two to three new patients and the workload is quite small, our suggestion was to stop admitting new patients at the weekends. Unfortunately our proposal was declined and we are currently still working at the weekends. As our oncology department and our preparation unit will move to the main building at the end of this year and we will start preparing drugs for our haematology ward too, I think our workload will grow as well. There will be more need for preparations during the weekends.

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# Iron and erythropoiesis-stimulating agents in anaemia

Anaemia is a frequent and clinically relevant problem in patients with malignancy and may be aggravated in patients receiving chemotherapy. Blood transfusions, iron supplementation, and erythropoiesis-stimulating agents (ESAs) are established treatment options for anaemic patients.

## Introduction

In the last two decades, ESAs have been the primary treatment for cancer-related anaemia. The ESA usage in the US increased 340% between 2001 and 2006 and, in Europe, their use has increased more than 50% between 2001 and 2006 [1]. A retrospective study using electronic medical records has shown that, in 1,731 patients with malignancy and receiving chemotherapy, ESAs were used in 55.8–68.9% of patients with haemoglobin (Hb) values < 11 g/dL ESA, which probably reflects the 2002 American guideline recommendations [2].



Thomas Rath  
MD

## Guidelines

In 2007 and 2008, the European and American guidelines for the management of anaemia in patients with cancer were updated. Both guidelines recommend the use of ESAs in anaemic patients with malignancy and chemotherapy with only small differences in Hb threshold for initiating ESA therapy.

The working party of the European Organisation for Research and Treatment of Cancer states that ESAs reduce the number of transfusions required and significantly improve the quality of life (QoL) in patients with chemotherapy-induced anaemia. Therefore, ESA therapy should be initiated when the Hb level is in the range of 9–11 g/dL with a treatment target of 12 g/dL [3].

In 2008, the American Society of Clinical Oncology (ASCO)/American Society of Hematology recommended initiating therapy with ESAs only for patients with chemotherapy-associated anaemia as Hb approaches, or falls below 10 g/dL aiming also for a target of 12 g/dL. The Society also commented on the lack of conclusive evidence regarding patient survival and improvement of QoL [4].

## Anaemia management in nephrology

In the field of nephrology, epoetin-alfa was approved for the therapy of renal anaemia in 1989. Subsequently, the usage of ESAs as a new therapeutic class became standard in the care of anaemic patients with renal insufficiency or on dialysis. Nevertheless, extensive scientific discussion regarding dosage, application, concomitant therapy, costs, and influence on survival or QoL developed in the renal community.

After publication of the National Kidney Foundation-Dialysis Outcomes Quality Initiative's Clinical Practice Guidelines for the Treatment of Anaemia of Chronic Renal Failure, [5] the European

Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure attempted to reflect the European clinical practice and experience in the years 1999 and 2005 [6, 7]. Although the guidelines were widely accepted, only 66% of the European patients on dialysis achieved the recommended Hb levels of at least 11 g/dL. In addition, only 48% of all patients had adequate iron stores, despite recommended iron substitution [8].

In the more recently-published 18-month observational GAIN study (Gain effectiveness in Anaemia treatment with NeoRecormon [epoetin beta]) in more than 4,000 patients on haemodialysis only 62% of patients reached the recommended target range of 10–12 g/dL Hb. In addition, the GAIN study again revealed the dose-sparing effect of subcutaneously applied epoetin compared to intravenously given epoetin [9].

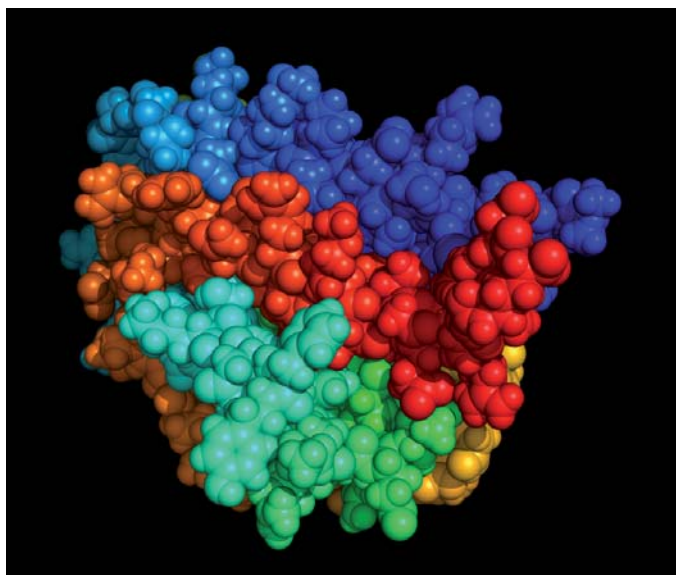
## Intravenous iron in nephrology

Intravenous iron supplementation is, in addition to erythropoietin treatment, a basic principle in the therapy of patients with renal anaemia and receiving haemodialysis. Current European guidelines recommend a target Hb concentration > 11 g/dL. Therefore, patients should be in iron balance with serum ferritin > 100 µg/L and a percentage of hypochromic red cells < 10%, or transferrin saturation > 20%, or reticulocyte Hb content (CHr) > 29 pg/cell. Achieving these target parameters demands iron supplementation in most patients on dialysis [10].

There has been concern about safety issues in the use of IV iron, especially with respect to major adverse events including anaphylaxis with iron dextran. However, it should be highlighted that these results predominantly account for adverse drug events that occurred following the administration of high-molecular rather than low-molecular weight iron dextran. The vast majority of studies on patient cohorts has not established a difference in the rate of adverse drug events between various available parenteral iron preparations [11–13]. Recently published studies are also showing positive effects of IV iron therapy either on parameters of iron storage, Hb concentration or erythropoietin usage, regardless of which formulation of parenteral iron was used [14, 15].

## Intravenous iron in oncology

Neither the European recommendations nor the guidelines of the ASCO comment extensively on the use of iron preparations in oncology [3, 4]; both state that IV iron preparation may be benefi-



cial or that iron monitoring may be valuable in treating the patients. Nevertheless, the usefulness of IV iron therapy in combination with ESAs in oncology is well known.

Intravenous iron, in addition to treatment with darbepoetin, can improve haematopoietic response rate and reduces the incidence of transfusion without compromising patient safety [16, 17]. The combined use of IV iron and epoetin beta in iron-repleted anaemic patients with malignancies leads to a greater increase in mean Hb from week eight onward compared to patients with epoetin beta 30,000 IU once weekly alone [18]. In addition, a cost-effectiveness analysis in Sweden disclosed better outcomes in anaemic cancer patients at lower costs compared to ESA treatment without intravenously-given iron [19].

In a prospective multicentre trial comparing no iron substitution versus oral iron versus standard IV therapy versus total dose IV iron in patients with chemotherapy-related anaemia and ESA therapy IV iron leads to increases in energy, activity, and overall QoL [20]. Also, in a recently published study in patients with chemotherapy-related anaemia the beneficial effects of adding IV iron to established ESA-therapy on achieving Hb response were confirmed [21].

### **Intravenous iron outside nephrology and oncology**

The combination of IV iron and recombinant human erythropoietin leads to a rise in Hb levels in patients with inflammatory bowel disease [22]. In the perioperative setting, and especially in elderly patients undergoing hip fracture surgery, IV iron reduces transfusion requirements and hastens recovery from blood loss [23]. The reported improvements in symptoms, functional capacity and QoL in patients with chronic heart failure are very interesting, irrespective of whether the patient is anaemic or not [24, 25].

### **Conclusion**

Anaemia is a relevant clinical problem in many patients. Structured iron management, especially the use of IV iron should be implemented in the routine care of all patients undergoing ESA treatment.

In routine clinical care, therapy with IV iron seems to be underused and the beneficial effects of iron possibly extend beyond that of anaemia therapy.

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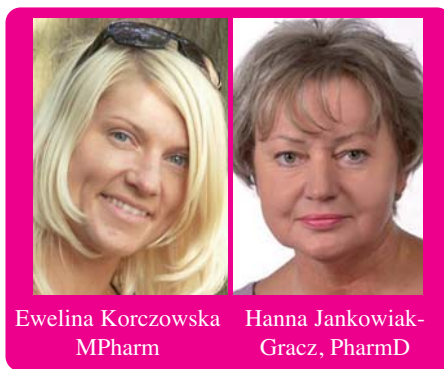


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# European use of devices supporting safe handling of cytotoxic drugs

A survey of current practice in safe handling of cytotoxics shows widespread use of a variety of protective devices.

In order to ensure maximum safety during the preparation of cytotoxic drugs special handling techniques and suitable equipment (designed to reduce the risk of exposure) must be employed. Numerous studies have confirmed that using special devices for reconstitution and administration of cytotoxic drugs reduces occupational contamination and exposure to these drugs. However, no matter how effective the device/system appears to be, it must be used within a ventilated laminar airflow safety cabinet or isolator with appropriate personal protective equipment and other safe handling practices. Nowadays pharmaceutical companies promote various devices for the reconstitution and administration of cytotoxic drugs, whose main aim is to prevent or minimise any possible contamination. In European countries several devices are available supporting safe handling of cytotoxic drugs. They are all helpful.



drugs, especially when a vial opening is too small, e.g. bortezomib, docetaxel, paclitaxel, vincristine, vinorelbine, or for monoclonal antibodies or liposomal products. In this situation the standard technique is to use a needle and Luer-lock syringe. About one third of respondents use special devices only for preparing some drugs, e.g. cyclophosphamide and iphosphamide, or for drugs in large volume vials, e.g. carboplatin, cisplatin, cyclophosphamide, ifosphamide.

A survey was conducted among European pharmacists to identify the use of devices supporting safe handling of cytotoxic drugs and assess current practice. Survey results were received from 45 hospital pharmacies between November 2009 and January 2010 (Poland 12, Portugal 5, Denmark 4, Greece 3, Hungary 3, Belgium 2, Czech Republic 2, Estonia 2, Spain 2, Switzerland 2, Bosnia and Herzegovina 1, France 1, Germany 1, Iceland 1, Italy 1, Luxembourg 1, Slovenia 1, Sweden 1).

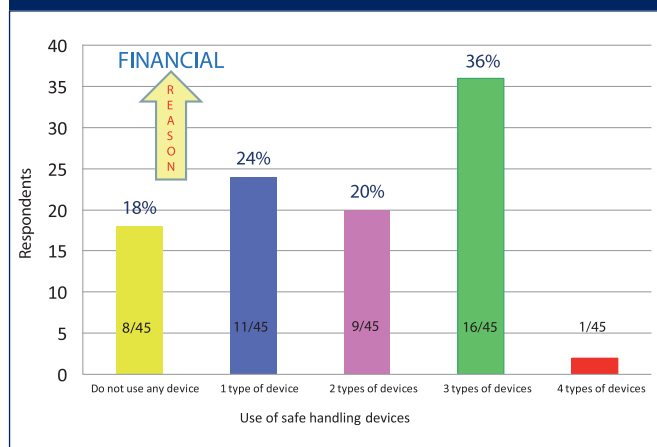
Eighty per cent of cytotoxic drugs are prepared in laminar airflow biological safety cabinets. Five respondents: Czech Republic (2), France (1), Spain (1) and Switzerland (1) reconstitute cytotoxic drugs in an isolator (in Czech Republic isolators must be used in a controlled area). Over 50% of respondents prepare between 15,000 and 40,000 doses of chemotherapy per year. In daily practice most respondents use three different types of devices, see Figure 1. There are mainly vented vial access devices and infusion bag access devices. Thirteen respondents answered that they use closed system drug transfer devices during the preparation and administration of cytotoxic drugs. Eight respondents do not use any devices either for reconstitution or administration of cytotoxic drugs. Survey participants were also asked what devices they use, see Figure 2.

More than 65% respondents use special devices both for reconstitution as well as administration of cytotoxic drugs. However, special devices are not used for reconstitution of all cytotoxic

In the opinion of almost all respondents, using the special devices during the reconstitution of cytotoxic drugs makes them feel safer and they can work more easily and faster.

In some countries (Bosnia and Herzegovina, Greece, Hungary) special devices for safe handling are not widely used, mainly because of the cost. The 20 French regional cancer centres have

Figure 1: Number of different types of devices used for reconstitution and administration of cytotoxic drugs

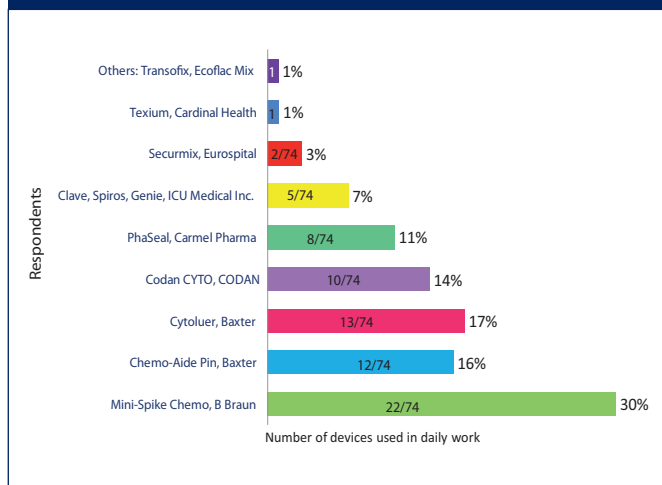


recently assessed the different devices available in order to choose some of them (group purchasing approach). In Spain, the law advises the use of closed systems.

The survey showed that in most European countries a number of devices supporting safe handling of cytotoxic drugs are used. Accessibility and the level of use differ. The most often used are devices for reconstituting cytotoxic drugs (mainly vented spikes).



**Figure 2: Number of devices used for reconstitution and administration of cytotoxic drugs**



It would also be valuable to repeat this survey in a few years, and to track the practice of using devices supporting safe handling of cytotoxic drugs over time.

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## Iron and erythropoiesis-stimulating agents in anaemia

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# Current situation of cytotoxics preparation in Europe – an ESOP online survey

This article summarises the results of a recent ESOP online survey from 20 European countries, conducted to determine how cytotoxic drugs are being prepared.

Although there are established guidelines for the safe handling and preparation of cytotoxic drugs, there may be differences in implementation of these guidelines in different countries. To obtain a more detailed picture about the current practices of cytotoxic drug preparation in Europe, an online survey was conducted via the ESOP website (www.esop.eu).

This survey addressed 2,125 ESOP members between January and April 2010. In this period of time, 129 questionnaires were returned from 20 different EU countries, corresponding to a response rate of ~ 6%.

The first two questions, of six in total, were rather general questions concerning the preparation facilities and annual number of preparations. Results revealed that 125/129 pharmacists do have the possibility to prepare chemotherapy under safe conditions and only four prepare chemotherapy on the ward. The majority (44%) of the interviewees work at large hospitals with more than 10,000 preparations per year, see Figure 1.

The next question concerned the annual percentage of discarded preparations caused by either therapy delay or because the patient did not turn up for treatment. The given percentages ranged from 0–15%, but most interviewees answered with ‘up to 1%’. Compared to the annual number of preparations, the amount of discarded therapies is quite low. Upon analysing the

data, the survey showed that the rate of discarded chemotherapies does not increase with the number of annual preparations. Hospitals with more than 10,000 preparations per year have their peak of discarded chemotherapies at ‘up to 1%,’ which is the same as hospitals with fewer annual preparations.

‘Do you prepare chemotherapy in advance?’ was the topic of the next question and was answered ‘Yes’ by 54%. Forty-four per cent of the interviewed pharmacists do

not prepare in advance and 2% only prepare chemotherapy in advance by way of exception. The timeframe for preparations in advance ranged from one to seven days, whereas the majority (48%) prepare infusions one day ahead of administration followed by 23% who work with two days. According to the survey, there was no correlation between the number of days of preparations in advance, and the rate of discarded treatments. Preparations in advance, ranging from one to seven days, all had their peaks in the category ‘up to 1%’.

According to the *European Pharmacopeia* it is permissible to use a maximum tolerance limit of 5% differentiation between the calculated dose and the dose prepared. The next question was whether this tolerance limit is used in practice and 102/129 pharmacists answered that they do work with these limits, whereas 27 pharmacists answered they do not use tolerance limits at all. The majority of pharmacists using tolerance limits stay within the given tolerance limit of maximum 5% and only a few pharmacists work with higher tolerance limits (see Figure 2).

The decision on tolerance limits is usually made between pharmacists and oncologists or is in line with the *European Pharmacopeia*, but can also be made using other methods like IT systems, e.g. Cato, Cypro, or Zenzy; the oncologists alone or due to practicability.

This survey has shown that safe handling of cytotoxics is an important issue and the quality standards set up for safe handling of cytotoxics seem to be broadly implemented in Europe. The preparation of chemotherapies is mainly performed in large hospitals, which follows the trend of having centres of excellence for the treatment of cancer. This fact, and the information that the majority of the interviewees prepare chemotherapies at a maximum of two days in advance, allows us to infer that these pharmacies have a huge amount of daily throughput. Economic vial sizes and easy-to-use products, as well as sufficient solution stability data for infusions, could therefore be of great help to make the daily routine of an oncology pharmacist easier.

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MPharm

Figure 1: Annual number of chemotherapy preparations

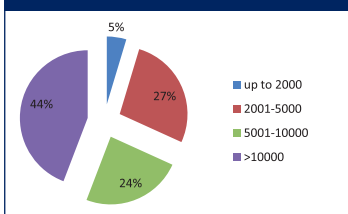
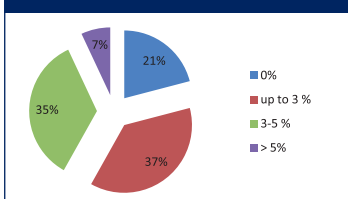


Figure 2: Accepted tolerance limits



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# Chemotherapy-induced nausea and vomiting: what are the best treatments

The treatment of chemotherapy-induced nausea and vomiting (CINV) has advanced considerably in recent years. The availability of the second-generation 5-HT<sub>3</sub> receptor antagonist palonosetron and the NK1 receptor antagonists has significantly improved the clinical efficacy of anti-emesis. These drugs form a key part of the latest European (ESMO) guidelines on the best management of CINV.

Despite the significant progress made after the introduction in clinical practice of the first 5-HT<sub>3</sub> (serotonin-3) receptor antagonists in the late 1980s, followed in 2003 by the neurokinin-1 (NK1) receptor antagonists, chemotherapy-induced nausea and vomiting (CINV) remain potentially distressing side-effects of cancer chemotherapy. Four selective first-generation 5-HT<sub>3</sub> receptor antagonists have become available for use in North America and/or Europe for the prevention of CINV: dolasetron, ondansetron, granisetron and tropisetron. Although these agents present some pharmacological differences in 5-HT<sub>3</sub> receptor binding affinity, selectivity and metabolism, these minor variations have not resulted in clinically significant differences in efficacy amongst them. Therefore they are considered equivalent in terms of efficacy and are therapeutically interchangeable when used at equipotent doses [1].

The introduction of palonosetron represents a significant progress in 5-HT<sub>3</sub> receptor inhibition to treat CINV. Palonosetron is a highly potent, selective, second-generation 5-HT<sub>3</sub> receptor antagonist with a pharmacological profile that is distinctly different from the other 5-HT<sub>3</sub> antagonists. Firstly it has a 5-HT<sub>3</sub> receptor binding affinity that is 100-fold higher than other 5-HT<sub>3</sub> receptor antagonists (pK<sub>i</sub> 10.5 compared with 8.91 for granisetron, 8.81 for tropisetron, 8.39 for ondansetron, 7.6 for dolasetron). For this reason, a typical dose of palonosetron is a factor 100 lower than the other 5-HT<sub>3</sub>-antagonists. Secondly palonosetron has an extended plasma elimination half-life of approximately 40 h, significantly longer than others in its class (ondansetron, 4 h; tropisetron, 7.3 h; dolasetron, 7.5 h; granisetron, 8.9 h) [2]. Thirdly palonosetron appears to have a different pharmacological mode of action. As well as published data on its positive cooperativity, allosteric binding and the receptor internalization, a recent publication on palonosetron in cell-culture and rats suggests it uniquely inhibits 'crosstalk' between 5-HT<sub>3</sub> and NK1 receptor pathway [3]. In summary Palonosetron appears to have unique interaction with the 5-HT<sub>3</sub> receptor at the molecular level, differentiating it from older 5-HT<sub>3</sub> receptor antagonists. This pharmacological data may provide a rationale for accumulating clinical data showing an extended efficacy observed with palonosetron in the delayed phase (24–120 hours post chemotherapy) [4].



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Another major development in treating CINV to emerge since 2003 involves targeting the NK1 neurotransmitter receptor. The NK1 receptor can be targeted using aprepitant and fosaprepitant, potent and selective antagonists with antiemetic activity when added to a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone in some chemotherapeutic settings [5].

In June 2009 the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) organised the third Consensus Conference on antiemetics in Perugia, Italy. The results of the conference have been recently published as part of the 2010 ESMO Clinical Recommendations in *Annals of Oncology* [6]. The updated MASCC/ESMO guidelines clearly indicate an individualised approach to CINV that takes into consideration the inter-patients variability (in particular whether the patient experiences acute or delayed CINV) and the differences amongst drugs given for cancer therapy that cover a wide spectrum of emetogenicity from minimal to high. The 2009 MASCC/ESMO guidelines have introduced relevant changes from the previous version following results from phase III trials on palonosetron and (fos)aprepitant. A NK1 receptor antagonist (fos)aprepitant is recommended in association with a 5-HT<sub>3</sub> receptor inhibitor plus dexamethasone for prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy (HEC). In moderately emetogenic chemotherapy (MEC) the guidelines now indicate a specific 5-HT<sub>3</sub> receptor antagonist, palonosetron, plus dexamethasone as the treatment of choice for the prevention of acute nausea and vomiting induced by non-AC (combination of an anthracyclines—doxorubicin or epirubicin—and cyclophosphamide). Moreover even for AC MEC chemotherapy palonosetron 'is the preferred 5-HT<sub>3</sub> receptor antagonist' if the NK1 receptor antagonist is not available. [6]. At present, no randomised study has investigated palonosetron in combination with a NK1 receptor antagonist so far. Furthermore, MASCC and National Comprehensive Cancer Network guidelines also suggest that IV palonosetron may be used prior to the start of a three day chemotherapy regimen instead of multiple daily doses of oral or IV 5-HT<sub>3</sub> receptor antagonists [6, 7].

In clinical trials palonosetron induces more protection from delayed emesis than 5-HT<sub>3</sub> antagonists with its shorter half life which could explain a higher acquisition cost. Evidence is emerging that better control of delayed emesis from the first

cycle of chemotherapy will reduce the number of uncontrolled CINV events and consequently the economic burden of CINV [8]. It is tempting to speculate that some differences in the mechanism of action of palonosetron as compared with those of other serotonin antagonists could provide a rationale for additional activity with this agent even in the challenging area of refractory emesis. However, we have to await the results of the clinical trials that substantiate this and then a more detailed assessment of the pharmacoeconomic impact of this approach can be performed.

In conclusion, current guidelines are based on an individualised approach to CINV. The availability of newer agents such as the second-generation 5-HT<sub>3</sub> receptor antagonist palonosetron and the NK1 receptor antagonists have significantly improved the clinical efficacy of anti-emesis and changed the previous use. All the professionals involved in the care of patients undergoing chemotherapy should be fully aware of those updates and transfer them to their clinical practice. The ESMO clinical recommendations can be freely downloaded from the ESMO-website ([www.esmo.org](http://www.esmo.org)).

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#### Comment

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## Motivating cancer patients by personality type

Professor Günther J Wiedemann, MD, PhD

It is important to motivate patients to take their medication. This article summarises different personality types and six principles of counselling.

“The good physician treats the disease. The great physician treats the patient who has the disease.” (William Osler, 1849–1919).

The safety of cancer patients prescribed antineoplastic drugs as an outpatient treatment strictly depends on the patients' compliance to the information given by physicians and other healthcare professionals. It has been shown in several large scale studies that at least one-third of all cancer patients do not take their vital medication and, as one study indicates, this non-compliance is partially due to insufficient information from pharmacists [1]. It is therefore important to increase patient support and compliance by improving consulting skills. This article summarises some principles of counselling that apply to both physicians and pharmacists and focuses on how to motivate your cancer patients by their personality type. The approach to the patient should consider factors like gender, age, social status and state of mind, but every consultant

should be aware that communication includes several aspects:

- facts (what you want to inform the patient about);
- self-presentation (what you want to communicate about yourself);
- relationship clues (how you think and feel about the patient);
- appeal (what you want to achieve).

Aspects of the **individual character** of the cancer patient should not be neglected. Personality traits can roughly be summarised to five motivational types, according to the psychological types developed by Mr Carl Gustav Jung [2] and Mr Werner Correll [3]. These are summarised later in this article.

#### Six important principles of consulting

##### Principle 1: Knowing, not guessing

For the majority of diagnostic and therapeutic procedures, a certain level of evidence is accepted [4]. A consensus according to



specific criteria, such as consistency of study results, clinical relevance of endpoints and risk-benefit ratio, leads us from evidence to recommendations. Use these recommendations.

**Principle 2: Individualise evidence-based therapies**

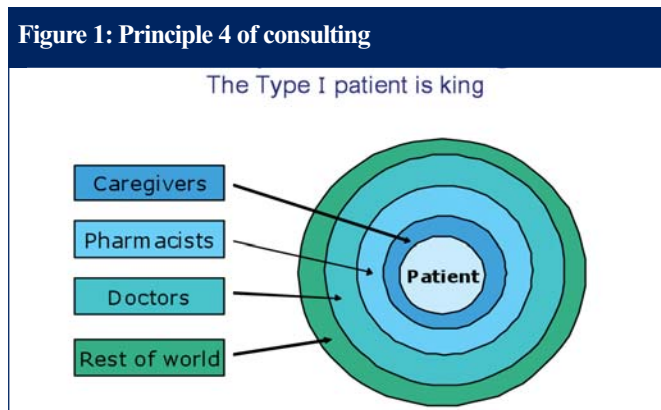
Two out of three cancer patients are over the age of 65 years old and treatment in the elderly is very complex. It is important to **know the drugs** that require dose modification in renal dysfunction, are affected by changes in hepatic metabolism and those which cause significant cardiotoxicity.

**Principle 3: Avoid conflict**

In order to individualise standard therapy if the patient does not agree, use a combination of all communication aspects.

**Principle 4: Always serve the Type I patient first**

See Figure 1.



**Principle 5: Advise Type III personally**

**Principle 6: Keep smiling! Yes, you can!**

Summarised below are some observations of each type of patient to look out for and the motivational strategy you should follow.

**TYPE I is motivated by social prestige**

- Impression: striking, fashionable
  - Communication: self-focused, loud
  - Behaviour: proactive, dominant
  - Hobbies: extravagant
  - Type: the 'loudmouth'
  - Attitude: optimistic, naive, know-it-all
- ⇒ Motivational strategy: emphasise prestige and exclusivity.

**TYPE II seeks security**

- Impression: conservative, unsophisticated
- Communication: humble, quiet
- Behaviour: flexible, reserved
- Hobbies: crafting, collecting
- Type: fearful
- Attitude: fear of undesired side effects and uncertain treatment outcome are more important than comfort. Test question: 'Would you be scared of vomiting your pills?'

⇒ Motivational strategy: emphasise functionality and security of the treatment

**TYPE III is motivated by personal attention and trust**

- Impression: conventional, safe
  - Communication: focused on other people, friendly
  - Behaviour: co-operative
  - Hobbies: family, clubs
  - Type: the follower
  - Attitude: 'in the moment'. 'If it helps others, it will help me, too.'
- ⇒ Motivational strategy: emphasise authority and similar cases

**TYPE IV: self-respect is most important**

- Impression: correct, orderly
  - Communication: punchy, determined
  - Behaviour: pedantic, uncompromising
  - Hobbies: involved, fanatic
  - Type: the 'bean counter'
  - Attitude: pessimistic. 'This needs a much more detailed explanation.'
- ⇒ Motivational strategy: use humourless and unambiguous language. Give the treatment plans in writing and provide precise and detailed information.

**TYPE V is a rational, tolerant and positive type who appreciates independence and responsibility**

- Impression: casual, sloppy
  - Communication: rational, determined
  - Behaviour: tolerant, constructive
  - Hobbies: many hobbies, travelling
  - Type: the cool girl/ guy
  - Attitude: positive 'Let's discuss details later.'
- ⇒ Motivational strategy: explain the 'big picture'.

You should be aware that conflicts with patients might result from incompatible personalities. Pairs of personality types commonly in conflict are Type I and IV and Type III and IV. Look carefully at the different types – which type are you?

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