Standards, like everything else, develop because we need them.

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**Conference Report**

The American way of funding for cancer research saves lives. Where are the Europeans?
The patient is the focus of our attention. This is a view with which everyone will surely agree, although at times some may be tempted to add ‘ultimately’. Ultimately it is not enough to recognise the importance of the principle; we also require the capacity – technical and economic – to implement it.

The European Union has again identified new members who are keen to join, as are their people. Since 2000 ESOP has been experiencing growing affinity with many experts involved in oncology pharmacy, calling on all of them to participate actively in the unification process.

Such was the spirit at the first Conference on Quality Standard for the Oncology Pharmacy Service (QuapoS) in September 2001 in Luxembourg. Standardisation, as we realised early on, is both an enormous challenge and an opportunity for oncology pharmacy. This spirit is alive and the participants of the workshops in 2004 and 2008 have continued in their mutual exchange. The fruits of this spirit lie not only in harmonisation and the benchmarking that result, but also in the freedom we have to develop in accordance with our local conditions – usually dependent on our social framework – and to identify and record differences.

For as we know, standards are not just about the identical things we have in common, but also about things that will remain different in future. Nothing is more depressing than attending courses or congresses that describe situations elsewhere that seem seductively desirable, but that cannot be implemented under conditions back home, in either the near or distant future. Sticking to ‘the devil we know’ is often the regrettable consequence.

QuapoS, developed by German hospital and public oncology pharmacists who were members of the German Association for Oncology Pharmacy (DGOP), should be seen as a symbol of progress.

The first quality standard was published in 1997 and concentrated primarily on pharmacy services in the narrower sense, i.e. conditions to comply with in the production of cytotoxic substances.

In 2000 the second edition reaffirmed and extended existing guidelines. It also incorporated services provided by oncology pharmacists as partners within an interdisciplinary team treating the patient. Furthermore, DGOP began certifying oncology pharmacy departments in pharmacies on the basis of QuapoS.

In the third edition, the field of pharmaceutical care was comprehensively examined. A holistic view of the patient and the orientation of pharmaceutical services toward the patient have now been reflected in the quality standard.

Now in the fourth edition we have incorporated the results of the Luxembourg Conference for Standardisation in Oncology Pharmacy working groups from 2001 to 2008. In addition patient demands have been given more consideration.

Let me emphasise once more that the aim of QuapoS is not to apply German findings to the rest of the world. Rather we are attempting to approach any interested parties in their home country and in their own language, and to facilitate their entrance into the European debate. We are fully aware that the English language will be the bridge linking us in our common scientific purpose.

Now the QuapoS and the commentary of 40 well-known experts are published in English. As the next step, the translation of the QuapoS into 23 languages will be presented at the 15th European Cancer Conference in Berlin, Germany.

I wish to express my gratitude to the delegates, members and friends who have made all this possible.
ESOP Masterclass report

The first part of the second series of Masterclasses in Oncology Pharmacy entitled Preparation of antineoplastic drugs took place in Prague, Czech Republic, at the beginning of December 2008.

This is the course organised by the ESOP that was first held in Denmark in 2007. In 2008 it was headed by Irena Netíková, Chairman of the Oncology Pharmacy Working Group in the Czech Republic. Organisational support was provided by Aesculap Academy of B Braun Medical.

A total of 38 participants from 14 European countries and one non-European country took part in the course. These pharmacists work mostly in central departments of cytostatics preparation or as clinical oncology pharmacists in hospital wards. The Czech Republic was represented by seven participants. The course took the form of lectures, seminars and workshops on current and much debated themes in the field of oncology pharmacy, such as quality standards in oncology pharmacy, contamination by cytotoxic drugs, organisation and building of a cytotoxic preparation unit, the effect of cytotoxic drugs on personnel health, good manufacturing practice, spill management, clean working procedures, devices for cytotoxic preparation, stability of prepared doses of cytotoxic drugs and information sources, etc. (see Figure 1).

A representative of B Braun Medical presented information about the CytoCare robotic system to participants. This system can prepare cytostatic drugs under aseptic conditions and with maximum safety for workers.

A good time was had by all, especially at the social evening whose theme matched the date of the course – St Nicolas.

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News Flash

New bone loss prevention agent
The New England Journal of Medicine has published two randomised placebo-controlled studies of denosumab, a novel human monoclonal antibody, for the treatment and prevention of postmenopausal osteoporosis and for the treatment and prevention of bone loss in men receiving androgen-deprivation therapy for prostate cancer.

The first study showed that denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of fractures in postmenopausal women with osteoporosis. The second study found that denosumab increased bone mineral density at the lumbar spine, femoral neck and hip, and reduced the incidence of new vertebral fractures among men receiving androgen-deprivation therapy for non-metastatic prostate cancer; 1,468 patients were randomised to 60 mg denosumab subcutaneously every six months or placebo (734 patients in each group).

The FDA has identified safety issues and may require a risk mitigation strategy before approving the agent. Nevertheless, Amgen has also submitted marketing applications for denosumab for prostate and breast cancer bone loss in Australia, Canada, the EU and Switzerland.


EJOP – Call for papers

The main objectives of the European Journal of Oncology Pharmacy (EJOP) are providing information on current developments in oncology treatment, sharing practice related experiences as well as offering an educational platform via conference/seminar reports to practising oncology pharmacists and pharmacy technicians. The editorial content covers scientific, clinical, therapeutic, economic and social aspects. Prospective authors are welcome and invited to share their original knowledge and professional insight by submitting papers concerning drug developments, safety practices in handling cytotoxics and breakthroughs in oncology treatment along with practice guidelines and educational topics which fall within the scope of oncology pharmacy practice. Manuscripts must be submitted in English, the journal offers English support to the manuscript content. The EJOP ‘Guidance for Authors’ can be found on the website (www.ejop.eu), where the journal is freely available in PDF format. You are encouraged to discuss your ideas for manuscripts with us at editorial@ejop.eu.
Determinants of attendance at cervical cancer screening and HPV vaccination clinics

Attendance both at screening and at HPV vaccination clinics is best predicted by attitudinal factors. Positive connotations of cancer prevention measures and utility expectations, fear of cancer and high subjective risk perception are conducive to attendance at screening and Human Papillomavirus (HPV) vaccination.

Introduction

For most cancer sites, survival in countries from Northern Europe, that is the ScanBalt region, is substantially higher than in other parts of Europe [1]. Furthermore, relative survival is also better in female than in male patients and decreases with age. This ScanBalt study sought to find out whether this was related to general health-related economics or a particular attitude of young women in the ScanBalt region towards cancer prevention, thus contributing to the European Regions of Knowledge strategy.

The introduction of the Human Papillomavirus (HPV) vaccine makes it possible for the first time in the history of cancer prevention to combat the major cause of a cancer before it has started. The secondary prevention measure of cervical cancer (screening) has thus been complemented by a primary prevention measure (vaccination).

Although studies on causes of attendance and non-attendance at screening do exist, very few are based on representative data for women of different ages, and multicausality is not taken into account. Some studies suggest that women of higher socioeconomic status attend screening more regularly than women of lower socioeconomic status [2]. The role of fear or anxiety is controversial. While most studies consider fear to be a barrier to screening do exist, very few are based on representative data for women of different ages, and multicausality is not taken into account. Some studies suggest that women of higher socioeconomic status attend screening more regularly than women of lower socioeconomic status [2]. The role of fear or anxiety is controversial. While most studies consider fear to be a barrier to attendance, others suggest that anxiety is predictive of higher screening attendance [3]. A lack of awareness of risk factors and prevention options is also believed to correlate with lower uptake [4, 5]. Knowledge of cervical cancer and HPV tends to be low overall, as various studies have shown [6–8].

Since the autumn of 2006, women have had the option of seeking vaccination against HPV. Infection with HPV is the main risk factor for developing cervical cancer and also a sine qua non [9, 10]. As various HPV types are also a causative factor for several other forms of cancer (oropharyngeal, anal, penile, vulvar and vaginal cancers), the vaccination truly marks a milestone in cancer prevention research [11–13]. Since March 2007, HPV vaccination against the virus types causing cervical cancer has been officially recommended for girls aged 12 to 17 by the German Standing Vaccination Committee (STIKO). Statutory health insurance providers cover the cost of HPV vaccination for this age group and beyond, in some cases up to the age of 26. As all authorities and professional associations underline, annual screening attendance is necessary despite vaccination because of the residual risk of becoming infected with other potentially carcinogenic HPV types not covered by the vaccine and due to the possibility of having been infected with the high-risk HPV types prior to vaccination [15].

The aim of our study was to analyse the determinants of uptake of preventive measures against cervical cancer as a basis for comparing the determinants of screening attendance with those of HPV vaccination attendance.

A population-based representative survey comprising 760 randomly selected women aged 14 to 65 was performed in the German federal state of Mecklenburg-Western Pomerania. Prevention behaviour, attitudes towards cervical cancer screening and HPV vaccination, and knowledge about cervical cancer and HPV were probed by means of a structured questionnaire. Descriptive analyses and multivariate logistic regression analyses were performed to identify the determinants of screening and HPV vaccine uptake.

Results

Uptake of cervical cancer screening has a reported attendance of 72.8% within the recommended interval of 12 months. Young women aged 18 to 35 are significantly more likely to attend for regular screening. Socioeconomic status and educational attainment do not affect screening attendance significantly.

HPV vaccination is taken up by 68% of adolescents aged 14 to 17, 38.2% of women aged 27 to 35 would consider seeking vaccination against HPV. Unlike screening attendance, HPV vaccination uptake and approval are not as strongly correlated with socioeconomic status.

The main reasons for not attending cervical cancer screening have to do with good subjective health (66.3%), embarrassment (38.1%) and forgetting to make an appointment (27.7%).

The main reasons for not getting vaccinated are lack of information (55.3%), being sure of whether the vaccination is
needed (47.3%) and scepticism about the utility of the HPV vaccination (27.3%).

Discussing the determinants of screening uptake, regular screening attendance was best predicted by attitudinal factors, socio-structural characteristics and subjective risk appraisal. Fear and anxiety seem to encourage rather than hinder regular screening. Higher social class correlated significantly with more regular screening attendance.

Looking at the determinants of HPV vaccination attendance, women who express fear of screening results, have positive perceptions of cancer prevention measures and are willing to invest in their health through appropriate behaviour, are significantly more likely to seek vaccination against HPV.

**Conclusion**

These results stress the importance of attitudinal factors in prevention behaviour in general in accordance with Andersen’s behaviourial model as a theoretical foundation of personal health care [15]. Especially of interest are positive perceptions of cancer prevention measures and readiness to invest in health. Contrary to observations in previous studies, fear or anxiety boosts rather than hinders uptake. Social class and education level determine prevention behaviour in the multivariate setting to some degree; this means women from higher social classes and with higher education attend screening more regularly. However, the effect of social class is not as evident in the case of HPV vaccination. There is no trade-off between screening and vaccination: 93.3% of women are aware of the necessity of attending screening regularly even if vaccinated against HPV.

Uptake rates for existing primary and secondary prevention measures against cervical cancer can be enhanced by fostering perceptions of utility and positive perceptions of regular screening and becoming vaccinated against HPV. Elderly women in particular should be encouraged to attend screening by means of a recall system. Given the low overall level of knowledge about cervical cancer and its risk factors, there is a need for education about the necessity and utility of prevention to reach women of all social classes.

**References**

Drug interactions in cancer treatment: a potential role for oncology pharmacists

Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents.

Introduction
This short article cannot give a detailed understanding of special topics. It aims to give a wide overview of this area of interest and to invite pharmacists to include this into their work.

Patients with cancer are at particularly high risk of drug interactions as they are commonly given several drugs, including antineoplastics, hormonal and supportive drugs. The majority of cancer patients are elderly and require many different drugs for coexisting conditions such as cardiovascular, gastrointestinal and psychiatric disorders, so the adverse interaction rate increases among the elderly and those who take two or more drugs for the management of underlying illnesses [1]. The age-related decline in hepatic and renal function also reduces their ability to metabolise and eliminate drugs and increases the potential for toxicity. Improvements in laboratory analysis and early clinical testing have made the prediction of potentially clinically significant drug interactions possible but not all drug–drug interactions can be foreseen, and those that are predictable are not always inevitable. Nonetheless, awareness of the potential for these interactions means the risk can be minimised by selecting appropriate drugs and by monitoring for signs of interaction.

Drug interactions can be classified as pharmaceutical, pharmacokinetic, pharmacodynamic or a combination of mechanisms [2]. Although a drug–drug interaction is most commonly observed, various factors such as food, nutritional supplements, complementary alternative medicines and environmental factors can interact.

Pharmaceutical interactions
Pharmaceutical interactions occur when two or more chemically or physically incompatible drugs are prepared in the same container prior to parenteral administration, resulting in the degradation of one or more drugs. For example, a covalent mesna-platinum adduct is formed by adding mesna, a thiol compound, to a cisplatin solution [3]. Other observations include the precipitation of etoposide and paclitaxel after dilution in infusion fluids at low pH, as well as the rapid inactivation of mitomycin to inactive mitosenes if the drug is reconstituted in pH 4–5 fluids such as 5% dextrose [4]. Check the compatibility of anticancer drugs before administering them.

Pharmacokinetic interactions
Pharmacokinetic interactions arise when one drug affects the absorption, distribution, metabolism or elimination of another drug. For instance, drugs that inhibit the activity of drug-metabolising enzymes may effect the blood levels of other drugs. The classic illustration is a xanthine oxidase inhibitor, allopurinol, which can inhibit the oxidative catabolic conversion of 6-mercaptopurine and consequently increase its oral bioavailability dramatically [5]. In addition, drugs that increase or decrease gastrointestinal motility may have a major impact on the oral bioavailability of other drugs. Food–drug interactions can also occur and may affect the bioavailability of orally administered anticancer agents, delaying, decreasing or increasing their absorption.

Following absorption, drug distribution to the target site is directed primarily by the blood supply and the binding properties of the drug to plasma proteins. Competition for plasma protein binding can modify drug distribution. If two concomitantly administered drugs rely on binding to a similar plasma protein, plasma levels of unbound (active) drug may increase. Anticancer agents such as paclitaxel and etoposide, which are recognised to be highly protein-bound, could hypothetically interact with other highly protein-bound drugs such as warfarin, which may be used to prevent or treat deep vein thrombosis in cancer patients [6].

Pharmacokinetic interactions most frequently occur via induction or inhibition of metabolising enzymes, mainly the cytochrome P450 (CYP) enzymes in the liver. Co-administration of an enzyme-inducing drug with a substrate for the identical enzyme system can result in increased metabolism, and consequently reduced serum concentrations of the substrate. Drugs that inhibit CYP metabolism can also increase serum concentrations of substrates for the inhibited enzyme. Anticancer drugs that are totally or partially metabolised by CYP enzymes include cyclophosphamide, taxanes, etoposide, irinotecan, aromatase inhibitors, tamoxifen, vinca alkaloids, bicalutamide, imatinib, gefitinib and erlotinib [7, 8].

Levels of drug-metabolising enzymes may vary between patients. Genetic polymorphisms have been documented for a number of CYP isoforms, including CYP2A6, CYP2D6, CYP2C9 and CYP2C19, so these must be borne in mind when assessing the risk of drug–drug interactions. For example, tamoxifen requires metabolic conversion by the CYP system into anti-oestrogenic metabolites, which are more potent than the parent compound. These include N-desmethyltamoxifen, formed by CYP3A4, and 4-hydroxytamoxifen and endoxifen, formed by CYP2D6. The interpatient variability in the relative levels of these CYP isoforms...
affects the efficacy of tamoxifen and has a tremendous effect on treatment outcomes in terms of toxicity, breast cancer recurrence and mortality [9].

Having undergone metabolism, most anticancer drugs are eliminated by the kidneys. Substances that change kidney or hepatic functions can interfere with the elimination of other agents and their metabolites. Some drugs either compete for active secretion, or modify the activity of membrane transporter proteins such as ABCB1 in the renal tubules. Concomitant administration of verapamil, an inhibitor of ABCB1 and vinblastine, an ABCB1 substrate in mice, results in increased concentrations of vinblastine and its metabolites within the liver and kidneys [10]. Gefitinib, a recognised ABC transporter inhibitor, could also interfere with the renal and/or biliary excretion of irinotecan and SN-38, which would result in increased plasma concentrations and toxicity [11]. Inhibitory effects on the organic anion transporter-mediated renal excretion by non-steroidal anti-inflammatory drugs and probenecid are likely to cause drug interactions with methotrexate that can result in a severe and even life-threatening bone marrow suppression and acute kidney injury [12].

Pharmacodynamic drug interactions
Pharmacodynamic interactions generally result from co-administration of two or more drugs with similar mechanisms of action. Pharmacodynamic interactions can be broadly categorised as synergistic, antagonistic or additive [13]. Synergistic interactions occur when the effect of two drugs is greater than the sum of their individual effects. Synergistic effects can increase antitumour activity and may improve clinical outcome. Examples are CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for Non-Hodgkin’s lymphoma and CAF (cyclophosphamide, doxorubicin, SFU) for breast cancer. Combination regimens are frequently preferred to overcome resistance, minimise non-overlapping toxicity and maximise antitumour activity. Antagonistic interactions mean the effect of two drugs is less than the sum of their individual effects, as when corticosteroids are given with interleukin-2 [14]. Additive means the effect of two drugs is the sum of the effects of each agent. Additive effects that increase renal toxicity have been observed when cisplatin is given with other nephrotoxic agents such as aminoglycosides and amphotericin B.

An example: the right combination of treatments while minimising risks
A 42-year-old premenopausal female with stage II invasive ductal carcinoma of the left breast (ER/PR positive, HER2 gene amplified, nuclear grade 3) underwent modified radical mastectomy and axillary lymph node dissection. Subsequently, she received AC (doxorubicin + cyclophosphamide) x 4 followed by weekly paclitaxel and trastuzumab x 12. She then received trastuzumab every three weeks as a maintenance dose. In this case, there is a synergistic pharmacodynamic interaction between the monoclonal antibody trastuzumab and chemotherapy which has been confirmed by several adjuvant breast cancer trials in reducing disease recurrence in patients whose tumours overexpressed the HER2 protein. Prognosis for women with HER2-positive disease has improved substantially. However, trastuzumab and the anthracycline-based regimen might bear a risk of cardiotoxicity. Therefore, the ejection fraction should be measured at baseline, after the AC phase of the regimen and before the trastuzumab is added, and then after the taxane/trastuzumab and before starting the maintenance phase.

Conclusion
Healthcare professionals should always keep updating their knowledge to develop a better understanding of drug interactions and help improve the quality of care among cancer patients. If they are aware of possible drug interactions, oncology pharmacists can minimise these risks by recommending the most suitable drugs and by monitoring for signs of an interaction.

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References

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The risk of exposure to cytotoxic drugs may arise during the routine handling of drug vials, aseptic preparation or during administration. Numerous studies have shown that aseptic manipulation using a standard syringe and needle technique almost universally results in contamination. Droplets, leakage from vial stoppers after multiple punctures and aerosol generation resulting from increased pressure inside drug vials have also been observed.

There is no known threshold limit for exposure to cytotoxic drugs but even low-level exposure to cytotoxic drugs should be avoided as much as possible. It can be minimised or eliminated through proper handling and use of protective equipment. Nowadays pharmaceutical companies promote special devices for the reconstitution and administration of cytotoxic drugs. The main aim of these devices is to prevent or minimise any contamination. There is a variety of drug preparation and administration systems available today. However, before using any products, it is important to provide independent studies for each component of the system or device to validate its effectiveness.

The pharmacists from the Central Cytotoxic Department, Clinical Hospital of Poznań University of Medical Sciences, Poland, conducted simple in-house tests to evaluate the containment ability of drug transfer devices. We tested six different devices for the reconstitution and administration of cytotoxic drugs: Cytoluer and Chemo-Aide Pin by Baxter, Chemo Mini-Spike by B Braun, the Tevadaptor system by Teva Medical Ltd, Clave by ICU Medical Inc, PhaSeal by Carmel Pharma and NeoSpike Onko by Neo Care medical products.

Objective
The purpose of the study was to evaluate the effectiveness and efficiency of the six different devices for the reconstitution and administration of cytotoxic drugs. In addition, the drug transfer devices were compared with the conventional needle/syringe.

Methods
In the first part of our study we evaluated all these devices during the routine reconstitution of cytotoxic drugs such as carmustin, cisplatin, ciclophosphamide, cytarabine, dacarbazine, doxorubicin, etoposide, rituximab. Every device was evaluated for its simplicity and ease of manipulation. We were focused on the subjective assessment of these devices.

In the second part of our study we used a simplified test to examine the spill/leakage containment of a vial transfer device involving the use of a fluorescein dye. This test is quick, repeatable and easy to perform. We used a 10% fluorescein sodium solution (commercial vial, volume: 5 mL). One drop of fluorescein was added to 10 mL of 15% potassium chlorate solution using the drug transfer device. All devices were used...
as specified by the manufacturer’s instructions. Then, the simulated cytotoxic drug solution was prepared according to the pharmacy department’s standard operating procedures. Every stage of this test was repeated 10 times. After reconstitution, components of the system or devices were disengaged, observed and photographed under ultraviolet light to visualise fluorescein leaks or spills, see Figure 1.

The fluorescent solution was also used to evaluate a reconstitution procedure using the conventional needle and syringe, see Figure 2.

Results
Each device tested was different in approach, but all of them were easy to use with straightforward connections. They are needle-free devices and protect against accidental needle stick.

The fluorescein test showed that during all phases of drug reconstitution no fluorescein leaks or spills were observed on the outside of any drug transfer devices. In comparison, during the reconstitution of a simulated cytotoxic drug solution using the conventional needle and syringe, two visible drops of fluorescein were observed on the gauze pad (average areas of contamination were 4–10 mm).

Conclusion
Drug transfer devices play an important role in preventing inadvertent exposure to cytotoxic drugs and should be considered part of a comprehensive safety programme.

In the study with the fluorescein solution we confirmed that all drug transfer devices can protect the operator during the reconstitution of cytotoxic drugs. This test also showed that compounding cytotoxic drugs using traditional needle/syringe techniques is one of the riskiest points of occupational exposure due to vial over-pressurisation, which can lead to spraying and leakage.

At present, there is a need for ongoing reviews, independent studies and published clinical data to validate the effectiveness of every drug transfer device available on the market. However, before choosing the right drug transfer device pharmacists must also take into account other factors, e.g. worker acceptability and costs.

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References

The Infostab/Stabilis website: a tool for oncology pharmacists

The stability and compatibility of anticancer drugs is an important preoccupation for oncology pharmacists involved in the preparation of these drugs.

Introduction
The preparation of injectable anticancer drugs in the Centralized Intravenous Additive Service is one of the main responsibilities of the oncology pharmacist. To be able to prepare solutions in advance, he has to know the characteristics of each drug to determine the best storage conditions, and the compatibility of drugs with different containers and solvents. The oncology pharmacist also has to answer nurses’ questions about the compatibility of drugs to be administered intravenously to patients.

The information provided by pharmaceutical companies is often scanty and irrelevant to daily practice. The goal of this article is to present the usefulness of the Infostab website in resolving issues of the stability and compatibility of anticancer drugs. This tool was presented at the ESOP/NZW meeting in Hamburg, Germany, in January 2009.

What is Infostab?
Infostab is a French non-profit association dedicated to providing information about the stability and compatibility of injectable drugs. Its website opened in November 2006. Its main function is to host the free European Stabilis database. An original feature of the database is the use of pictograms as a universal language, although the text has been translated into all European languages.

Stabilis contains more than 380 monographs of injectable drugs with 65 anticancer drugs. It provides information about the stability in solutions and admixtures, incompatibilities and the factors affecting stability such as the solvent, the container, the temperature, the pH, etc. (see Figure 1).

A three-monthly newsletter is published. It contains information about new articles selected for Stabilis during the last three months, any changes to the database (new functions), new monographs, new pictograms, the posters concerning the stability of injectable drugs presented during recent congresses mainly in Europe, a list of new documents that can be downloaded on the website and visitor statistics by month and by language.

Stabilis contains also a search function for incompatibilities between numerous molecules. The user can enter their scientific or commercial names and Stabilis will verify all the known incompatibilities between these molecules.

Summary lists by theme are available: stability in various containers, drugs affected by light, incompatibility in various solvents, etc.

Stabilis is a tool for the daily practice of European oncology pharmacists. Currently, the statistics shows that the site is mainly used for drugs prescribed in oncology with 18 anticancer drugs amongst the first 20 consulted monographs. This represents more than 50% of the consultations.

Other functions of the Infostab website
The website provides news twice a week on Tuesday and Friday with stability studies, methods of assessing stability, congress announcements, etc. Posters and publications can be downloaded and there are links to the websites of other databases and guidelines.

So, add this website address to your favourites: www.infostab.com!

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Figure 1: Paclitaxel stability in solution

For example: line 5, Paclitaxel solutions stored in glass vials diluted in 0.9% sodium chloride (green triangle) at a concentration of 1.2 mg/mL at 25°C and protected from light are stable for 5 days. The information comes from reference 2172.
Neurotoxicity, a common side effect of cytotoxic therapy – how to protect the patient

Neurotoxicity is the second most frequent side effect of cancer therapy after haematological toxicity. Administration of cytotoxic drugs can cause central neurotoxicity or peripheral neuropathy.

Central toxicity
The most common diagnosis of central toxicity is ifosfamide-induced encephalopathy, which can occur in 5–30% of patients. Typical symptoms are disorientation, hallucination, catatonia and seizures, gradually worsening to coma and death. Risk factors include advanced age, hepatic and renal dysfunction, oral ifosfamide and concomitant use of other central nervous system (CNS) depressants [1]. However in our experience, patients with very active metabolism (especially young athletes) are under most threat.

Ifosfamide undergoes secondary metabolism to the dechloroethylated metabolites and chloroacetaldehyde. Chloroacetaldehyde is the metabolite responsible for nephrotoxicity and neurotoxicity by direct nerve damage, depletion of CNS glutathione level and inhibition of mitochondrial oxidative phosphorylation resulting in impaired fatty acid metabolism.

A simple, well-established solution is administration of methylene blue. Methylene blue restores and maintains mitochondrial respiration and therefore can be used to correct or prevent acute neurotoxic effects. IV administration of methylene blue is useful in the treatment of grade 3 or 4 neurotoxicity. Prophylactically methylene blue can prevent encephalopathy in high-risk conditions. However prophylactic or concurrent administration of methylene blue with ifosfamide requires further clinical evaluation [2, 3].

Because many patients in our hospital are at high risk and it is difficult to prepare methylene blue for IV administration, patients have been treated prophylactically with oral methylene blue and concurrently with ifosfamide for the last eight years.

R
Methylenii Caeruleum 0.2
Aqua destillata ad 20.0
Misce fiat solution
Dose 5 mL 3–4 times daily
Stability one month, protect against light

Peripheral toxicity
In contrast to ifosfamide-related encephalopathy, chemotherapy-induced peripheral neuropathy (CIPN) cannot be treated easily. Protective strategies are not effective enough and neuropathic symptoms can occur not only as a consequence of antineoplastic and other drugs, but as the result of cancer itself, or other diseases, e.g. diabetes.

Peripheral neuropathy symptoms are different according to the nerves affected. Sensory nerve damage causes pain, numbness and tingling, burning, prickling, pinching or a loss of feeling. Motor nerve damage manifests as weakness or paralysis of the muscles that control those nerves. Dizziness, constipation, difficulty urinating, impotence, vision changes and hearing loss are typical of autonomic neuropathy. Symptoms begin gradually. Prospective studies demonstrate that maximum symptoms and deficit may occur up to a month after discontinuation of treatment [4].

Symptoms reach a plateau at, or soon after, the end of treatment and improve after treatment is discontinued. There is often glove-and-stocking distribution of sensory loss and nerve hyperexcitability. Patients feel their skin is so sensitive that the slightest touch is agonising. They complain of heaviness or weakness in the arms and legs and an unsteady gait and can have difficulty feeling the floor beneath them. Neurotoxicity may develop as a consequence of treatment with platinum analogues (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinorelbine) and more recently thalidomide and bortezomib.

It is paradoxical that non-dividing neurons are susceptible to cytotoxicity. Long peripheral nerve axons are susceptible to agents that interfere with energy metabolism and axonal transport. Cytostatics can affect neuronal cell bodies in the dorsal root ganglion via transport deficits or energy failure and axonal membrane ion channel dysfunction. Patients treated with oxaliplatin have revealed alterations in axonal Na(+) channels. Binding of platinum to mitochondrial DNA is a potential mechanism underlying delayed neuronal death [5].
Peripheral neurotoxicity is a dose-limiting side effect related to cumulative dose and infusion duration. Individual risk factors may also affect the development and severity of neurotoxicity. As more effective multiple drug combinations are used, patients are treated with several neurotoxic drugs. Synergic neurotoxicity has not been extensively investigated yet. Underlying inherited or inflammatory neuropathies as well as focal radiotherapy or intrathecal administration may predispose patients to developing severe symptoms.

CIPN related to platinum compounds causes complaints of paresthesias in the distal extremities. All sensory modalities are involved, but loss of large fibre sensory function is often prominent. This may progress to severe sensory ataxia. The limiting dose for cisplatin is ≥400–500 mg/m², typically 3–6 months into treatment 60–80% of patients develop a stereotypical cold-induced acute toxicity that involves reversible paresthesias in the throat, mouth, face, and hands occurring within 30–60 minutes of oxaliplatin administration. Other alkylating agents such as cyclophosphamide, procarbazine and thiopeta can cause mild peripheral neuropathy. Paresthesias, pain in the feet and general sensory loss have occurred; recovery is slow and incomplete over years after drug withdrawal.

Mitotic spindle inhibitors vinca alkaloids, taxanes and podophyllin analogues (etoposide and teniposide) interfere with microtubule assembly and mitotic spindle formation. The disruption of microtubule function in axons also inhibits axonal transport. Sensory, motor and autonomic fibres are all affected. Because the cell body is usually spared, function can recover well, especially in children and young adults [6].

**Treatment of CIPN pain**
Pain relievers such as aspirin and ibuprofen can be used only for mild symptoms and are not very effective. More severe symptoms are treated with COX II inhibitors, e.g. nimesulid or preferably opioids (tramadol, oxycodone, morphine). Mild to moderate symptoms can also be treated by antidepressants (amitriptyline, nortriptyline, imipramine, citalopram, venlafaxine, paroxetine and bupropion). Antiepileptic drugs (carbamazepine, gabapentin, pregabalin, lamotrigine) are helpful for jabbing, shooting pain. Other drugs, like for example mexiletine, a drug normally used to treat irregular heart rhythms, may help to relieve burning pain.

**Prophylactic strategies**
Many clinical trials have attempted prophylactic treatment of CIPN with, e.g. amifostine, vitamin E and glutathione [7]. Unfortunately, a recent Cochrane review [8] concluded that there was insufficient evidence to recommend the use of any preventative treatment for platinum toxicity.

The experimental agents acetyl-L-carnitine (ALC), glutamate and glutamine have been studied intensively. ALC plays an essential role in intermediary metabolism. Its neuroprotective and neurotrophic actions, antioxidant activity, positive actions on mitochondrial metabolism, and stabilisation of intracellular membranes are still being investigated [9, 10]. Glutamate in animal studies significantly protected against both sensory and motor neuropathy. No intrinsic neurotoxicity and no interference with the cytotoxic efficacy of vincristine were observed [11, 12]. Glutamine has been tested as a neuroprotective agent in high-dose paclitaxel-induced peripheral neuropathy [13]. Using oral glutamine concomitant to chemotherapy significantly reduces the incidence and severity of peripheral neuropathy of patients receiving oxaliplatin without affecting response and survival [14, 15] (see Figure 1).

**Figure 1: Efficacy of 10% glutamic acid solution**

Patients had to choose one of three options: no reduction, mild reduction, good reduction of chemotherapy-induced peripheral neuropathy (CIPN) symptoms.

Ten percent glutamic acid solution is made in the General Teaching Hospital Prague and is being tested for CIPN symptoms after treatment with taxanes and oxaliplatin.

**R**

Acidum glutamicum 15.0
Sirupus plantaginis 45.0
Aqua purificata ad 150.0

Dose 10 mL three times daily

**Conclusion**
Neurotoxicity after cytostatics is a serious side effect, very often dose limiting and in advanced cases possibly demanding a change of chemotherapy. We can prevent central neurotoxicity after ifosfamide administration relatively well, but we are not able to prevent or to treat peripheral neuropathic symptoms. It is very important to continue clinical trials and research projects to improve supportive care in oncology therapy.

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References
Introduction
On 30 March 2009, FDA approved everolimus (Afinitor) for the treatment of refractory renal cell carcinoma (RCC) [1]. For Europe, the approval by EMEA is expected imminently (positive opinion by the CHMP dated 29 May 2009). The mechanism of action is relatively new in cancer therapy, since everolimus is only the second compound of this group reaching marketability. It is anticipated that the area of application will not be limited to RCC.

From Easter Island to mTOR inhibition
In the 1970s a new strain of the bacteria Streptomyces hygroscopicus was discovered in a soil sample taken from Easter Island. An antibiotic was isolated from this bacteria, and because of the Micronesian name of Easter Island, Rapa Nui, the new substance was called rapamycin. Rapamycin was identified as a potent antifungal agent. Later it was found to be also a potent suppressor of the immune system. Thus sirolimus (INN) was approved in 2000 by FDA and in 2001 by EMEA for the prophylaxis of organ rejection in patients receiving a renal transplant (Rapamune). Derivatives were also developed. One of them is everolimus, which was approved in 2004 in several European countries, but not in the US, for the prophylaxis of organ rejection in patients receiving a renal or heart transplant (Certican). At first, the mechanism of action of rapamycin and its analogues was not really clear. In 1993, during a screen for resistance to the antibiotic effect of rapamycin, it was found to bind to and inhibit two distinct enzymes in budding yeast, and so those enzymes were called ‘target of rapamycin’, TOR1 and TOR2 (Kunz et al., Helliwel et al., as cited in [2, 3]). Shortly afterwards, in 1994, a mammalian homologue was discovered, and as a consequence it got the name ‘mammalian target of rapamycin’ or mTOR (Brown et al., Chiu et al., Sabatini et al., as cited in [2, 3]). It was found that dysfunctions in the mTOR pathways were associated with several cancers. So the research on mTOR inhibitors such as rapamycin and its analogues got a new boost, and they were tested as potentially antineoplastic drugs. In 2007, the first rapamycin analogue got the approval for treatment of advanced RCC by FDA and EMEA: temsirolimus (Torisel). Everolimus is now the second mTOR inhibitor approved for cancer therapy.

Chemistry
As already mentioned, everolimus is a derivative of rapamycin, which is obtained via fermentation from a strain of the bacteria Streptomyces hygroscopicus. Rapamycin is a 31-membered macrolide, containing both a lactone and a lactam, and 15 chiral centres. Everolimus differs from rapamycin, as does temsirolimus, only in the substituent on the cyclohexane ring side chain, but while in temsirolimus the hydroxyl group on this cyclohexane ring is esterified with dihydroxyvaleric acid (2,2-bis(hydroxymethyl)propionic acid), in everolimus this hydroxyl group is etherified with ethylene glycol (see Figure 1). Therefore, everolimus can also be called a hydroxyethyl rapamycin. It is evident that an ether is much more stable than an ester.

Pharmacokinetics
Everolimus is administered orally. For detailed pharmacokinetic data compared to temsirolimus (see Table 1). A high fat meal reduced $C_{\text{max}}$ by 60% and AUC by 16% of the 1 mg dose. The blood-to-plasma ratio is concentration dependent. At blood concentrations observed in cancer patients following the recommended dose of 10 mg the blood-to-plasma ratio is about 20% [1].

Everolimus is a substrate of CYP3A4. Metabolites detected in human blood were scarcely active and included monohydroxylated and hydrolytic ring-opened products as well as a phosphatidylcholine conjugate. The main circulating compound is everolimus itself, accounting for about 40% of the AUC [1].

After hepatic metabolism of everolimus the metabolites are mainly excreted in the faeces. For patients with moderate hepatic impairment (Child–Pugh class B) the average AUC was found to be doubled which suggests a dose reduction to
5 mg. Everolimus should not be administered to patients with severe hepatic impairment (Child–Pugh class C). No dose reduction is required for patients with renal impairment [1].

**Mechanism of action**

Everolimus inhibits the so called mammalian target of rapamycin (mTOR). mTOR is a serine-threonine kinase, thus an enzyme catalysing the phosphorylation of proteins at amino acids serine and threonine, leading to activation or deactivation of this protein. mTOR exists in two distinct complexes, mTOR complex 1 and 2 (mTORC1, mTORC2). The two complexes are part of two contiguous, but distinct signalling pathways. It is remarkable that only mTORC1 is inhibited by rapamycin and its derivatives. However, recent investigations suggest that rapamycin can perturb mTORC2 assembly [2].

Everolimus does not bind straight to mTORC1. The real receptor for everolimus is the immunophilin FK506 binding protein (FKBP12), with which it forms a complex. This complex binds in the C terminus of mTORC1 called FRB (FKBP12 rapamycin binding), thereby inhibiting mTORC1 activity.

### Table 1: A comparison of everolimus and temsirolimus

<table>
<thead>
<tr>
<th>INN</th>
<th>Everolimus</th>
<th>Temsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>RAD001</td>
<td>CCI-779</td>
</tr>
<tr>
<td>Brand name</td>
<td>Afinitor</td>
<td>Torisel</td>
</tr>
<tr>
<td>Marketing authorisation holder</td>
<td>Novartis</td>
<td>Wyeth</td>
</tr>
<tr>
<td>FDA/EMEA approval</td>
<td>30 March 2009/</td>
<td>19 November 2007</td>
</tr>
<tr>
<td>Indication</td>
<td>Advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib</td>
<td>First-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors</td>
</tr>
<tr>
<td>Administration/dosage form</td>
<td>p.o./tablets</td>
<td>IV/concentrate and diluent for solution for infusion</td>
</tr>
<tr>
<td>Recommended dose</td>
<td>10 mg/day</td>
<td>25 mg/week</td>
</tr>
<tr>
<td>Regime</td>
<td>Continuous treatment</td>
<td>Continuous treatment</td>
</tr>
<tr>
<td>Available strengths</td>
<td>5 mg, 10 mg</td>
<td>30 mg/1.2 mL (25 mg/1 mL)</td>
</tr>
<tr>
<td>Storage</td>
<td>15–30°C Protect from light and moisture</td>
<td>2–8°C Protect from light</td>
</tr>
<tr>
<td>Shelf life</td>
<td>2 years</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>24 hours after reconstitution 6 hours (solution for injection)</td>
<td></td>
</tr>
<tr>
<td>Fraction absorbed</td>
<td>11%</td>
<td>n/a</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;* (h)</td>
<td>1 (0.5 – 2.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)*</td>
<td>64.4 ± 17.8</td>
<td>592.4 ± 101.9 (temsirolimus)</td>
</tr>
<tr>
<td>AUC (ng·h/mL)*</td>
<td>510.1 ± 165.8</td>
<td>2276 ± 340 (temsirolimus)</td>
</tr>
<tr>
<td>Clearance (L/h)*</td>
<td>20.6 ± 6.8</td>
<td>11.4 ± 2.4 (temsirolimus)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;(h)*</td>
<td>36.9 ± 9.5</td>
<td>17.7 ± 4.5 (temsirolimus)</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>None</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Steady state</td>
<td>Within 2 weeks</td>
<td>n/a</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>74%</td>
<td>87% (at 100 ng/mL)</td>
</tr>
</tbody>
</table>

* after single recommended dose in healthy subjects

mTORC1 is a downstream target of the PI3K-AKT signalling pathway, a key regulator of cell cycle proliferation, cell growth and survival as well as glucose metabolism. It is frequently deregulated at various points in a wide range of tumour types (see Figure 2). The key enzymes are PI3K and AKT. Activation of several receptor tyrosine kinases (RTKs), for example IGF-1R (insulin-like growth factor 1 receptor) or EGFR (epidermal growth factor receptor), leads, amongst others via the GTP-binding protein Ras, to activation of PI3K. The major downstream target of PI3K is AKT. The activation of AKT via PI3K can be inhibited by PTEN protein. The encoding gene PTEN is known as tumour suppressor gene, and its loss or mutation is associated with several human cancers. AKT can also be activated by mTORC2. AKT has several downstream targets. Amongst others it inhibits the TSC1-TSC2 complex. By suppressing the GTP-binding protein Rheb, TSC1/2 is a negative regulator of mTORC1. Since AKT inhibits an inhibitor of mTORC1, the bottom line of AKT-activation is mTORC1-activation.

Beside the PI3K-AKT pathway there is another pathway leading to inhibition of TSC1/2 (and therefore to activation of mTORC1): the activation cascade RTKs-Ras-Raf-MEK-ERK.

Various points of the pathways outlined are deregulated in several human cancers [3]. Some of them are marked in Figure 2. All of them cause (over)activation of mTORC1. The main downstream targets of mTORC1 are 4EBP1 and p70S6K1 (S6K1).

Phosphorylation of S6K1 by mTOR leads to activation. S6K1 has several targets, including ribosomal proteins such as S6, elongation factors and insulin growth factor 2. 4EBP1 is inhibited by mTOR through phos-
Preclinical efficacy

The arrest of G1 growth.

-eIF4E. Thus inhibition of mTOR activity by everolimus results in cell cycle progression and S-phase initiation via S6K1 and 4EBP1.

lates the translation of mRNA encoding proteins required for G1 phosphorylation and itself inhibits eIF4E. The mTORC1 pathway regulates the translation of mRNA encoding proteins required for G1 cell cycle progression and S-phase initiation via S6K1 and 4EBP1 -eIF4E. Thus inhibition of mTOR activity by everolimus results in the arrest of G1 growth.

Efficacy

Preclinical in vitro studies demonstrated that everolimus inhibits most (but not all) of human tumour cell lines tested. The antiproliferative effect did not correlate with inhibition of S6K1 and 4EBP1 activation, but very well with the levels of AKT Serine 473 phosphorylation and S6 Serine 240 and 244 phosphorylation [2].

In vitro studies also showed antiangiogenic activity and inhibition of endothelial cell proliferation.

In a first phase I study in patients with advanced solid tumours everolimus was given weekly. It was well tolerated at a dose from 5 mg up to 30 mg. A second phase I study evaluated how the phosphorylation of the downstream targets 4EBP1, S6K and eIF4E was inhibited by weekly doses of 20, 50 or 70 mg and daily doses of 5 or 10 mg. Doses of 10 mg daily and 50–70 mg weekly resulted in almost complete inhibition of phosphorylated S6K and phosphorylated 4EBP1.

In several phase II studies the 10 mg daily regimen was further evaluated.

Based on these studies a double-blind, randomised, placebo-controlled phase III trial was initiated in 2006 for treatment of advanced RCC after progression on sunitinib, sorafenib or both (RECORD-1 Study) [4]. At this time standard treatment for advanced RCC was therapy with sunitinib (Sutent), sorafenib (Nexavar) or bevacizumab (Avastin) plus IFN-α2a (Roferon-A) [7], since temsirolimus (Torisel) was not approved at this time. After failure or progression there were no therapeutic alternatives. Four hundred and ten patients were randomly assigned in a two to one ratio either to oral everolimus 10 mg per day or to placebo. Primary end point was progression-free survival (PFS). Crossover to open label everolimus after disease progression was allowed. Final analysis was planned after 290 progression events, but after the second interim analysis the study was terminated, because the pre-specified efficacy stopping boundary was crossed. At the time of data cut off median PFS in the everolimus arm was four months compared to 1.9 months in the placebo arm (independent central review). This effect was almost exclusively due to stable disease, partial response was only seen in three patients (1%). Quality of life was sustained during therapy with everolimus. Due to the concession of crossover it was not possible to assess a benefit in overall survival.

Adverse effects

The term ‘targeted therapy’ suggests that a molecule graced by this term affects only aberrant cells and has only few and moderate adverse effects. This has only been a theoretical approach so far, as the targets are also present in normal cells playing a role in homeostasis.

Some of the adverse effects of everolimus can be deduced from its mechanism of action. Since mTOR downstream targets are involved in glucose and lipid metabolism, potential increases in cholesterol, triglycerides and glucose are not surprising. In fact elevation of these parameters was found in over 50% by blood tests, but fortunately clinically significant cases can mostly be managed and severe effects are rare. Everolimus also acts as an immunosuppressant, which increases the risk of potentially severe infections, especially with opportunistic pathogens.

Other frequent or severe adverse effects cannot easily be deduced from the mechanism of action.

The most common (≥20%) adverse events observed in the RECORD-1 study were stomatitis (38%), anaemia (38%), asthenia (33%), diarrhoea (30%), cough (30%), rash (29%), nausea (26%), anorexia (25%), peripheral oedema (25%), pyrexia (20%), vomiting (20%), and hypercholesterolaemia (20%). The most severe (grade 3/4) adverse reactions were anaemia (10%), dyspnoea (8%), hyperglycaemia (6%), fatigue (6%), and lymphopenia (4%). Pneumonitis (3%), dyspnoea (3%), lung disease (1%), fatigue (1%) and renal failure (1%) were the toxicities leading to treatment termination [1].

One specific side effect needs a closer look: non-infectious pneumonitis is a known class effect of rapamycin derivatives. It was reported in 14% of patients, also occurring at grade 3/4 (4%). As
this side effect can be fatal, appropriate monitoring is recommend-
ed. But it is notable that new or worsening CT changes were reported in almost 50%, although clinically reported pneumonitis occurred in only 14%. So CT results are only a hint of, but not evidence for, this adverse effect.

**Drug interactions**
Everolimus is a substrate of CYP3A4 and the multidrug efflux pump PgP, so strong or moderate inhibitors of CYP3A4 and PgP should not be used together with everolimus. With strong inducers of CYP3A4 or PgP a dose increase of everolimus should be considered. On the other hand everolimus is also an inhibitor of CYP3A4 and PgP, but there were no clinically significant pharmacokinetic interactions found due to this mechanism [1].

**Future prospects**
**Other indications**
Beside the approved treatment of refractory RCC, everolimus is also being investigated for the treatment of several other cancers. Recently the results of a phase II trial have been reported: 145 patients with relapsed lymphoma were treated with everolimus. The overall response rate was 33%, in the subgroup with Hodgkin’s disease even 53%. Due to this outcome a phase III trial was initiated evaluating everolimus for adjuvant therapy in poor risk patients with diffuse large B-cell lymphoma [5].

Other phase III studies are investigating the efficacy of everolimus in the treatment of advanced gastric cancer, metastatic colorectal cancer, various neuroendocrine tumours and some benign tumours associated with tuberous sclerosis complex [6].

**Combination therapy**
Promising investigations deal with the combination of mTOR inhibitors with other antineoplastic agents. This is based on several rationales. The concept of vertical blockade means the use of agents inhibiting two or more different targets in the same signalling pathway with intent to break negative feedback loops. So the combination of everolimus with IGF-1R inhibitors showed an additive growth inhibitory effect [8]. The combination of everolimus with sorafenib (clinical trials phase I/II for RCC, hepatocellular carcinoma, lymphoma and multiple myeloma) is also in this category.

The most interesting concept deals with restoring sensitivity when drug resistance had occurred, for the PI3K-AKT and the Ras-Raf-MEK-ERK signalling pathways not only play a role in the onset of cancer but have also been implicated in multiple anticancer drug resistance. For example activation of AKT and/or PI3K is associated with resistance to trastuzumab, endocrine and paclitaxel therapy in breast cancer, to all trans-retinoic acid in leukaemia, to imatinib in gastrointestinal stromal tumour, to cisplatin in ovarian, uterine, lung and breast cancer and to etoposide and doxorubicin in gastric cancer. ERK activation is involved in resistance to cisplatin in ovarian cancer, tamoxifen in breast cancer, doxorubicin in prostate cancer, 5FU in pancreatic cancer and to vincristine in leukaemia [3] (see Figure 2).

The results of a phase II trial concerning the neoadjuvant combination of everolimus and endocrine therapy (letrozole) in ER-positive breast cancer showed an increased clinical response rate of 68.1% vs. 59.1% for letrozole monotherapy [9]. Other ongoing clinical trials are investigating the combination of everolimus with exemestane (phase III), trastuzumab (phase I and II), trastuzumab plus paclitaxel (phase I/II and III), and paclitaxel plus cisplatin (phase I and II) in breast cancer. A big phase III trial is exploring the integration of everolimus, bevacizumab and lapatinib into current neoadjuvant chemotherapy regimes for primary breast cancer [6].

**Conclusion**
Rapamycin and its derivatives offer hope in the treatment of several carcinomas, as the target, mTOR, is part of an important signalling pathway associated with cancer genesis and drug resistance. Everolimus is the first mTOR-inhibitor approved for antineoplastic therapy, that can be administered orally. It has also filled the gap in the treatment of RCC resistant to VEGF inhibitors, as temsirolimus is only approved for advanced, but not refractory RCC. If expectations are fulfilled in ongoing trials, a broadening of indications can be expected. Future investigations also may elucidate, if there are further important clinical differences between the rapamycin analogues.

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**References**
1. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000TOC.cfm
6. www.clinicaltrials.gov
ESOP is urging hospital pharmacists to collect evidence for the usefulness of uridine products for hand–foot syndrome. Could you arrange a clinical study to collect robust evidence in your hospital?

Palmar-planar erythrodysesthesia or hand–foot syndrome (HFS) is a side effect that can occur with several types of chemotherapy. For example, capecitabine, 5FU, doxorubicin and high-dose interleukin-2 can cause this skin reaction for some patients, 45–56% of all patients treated with capecitabine suffer from this syndrome. Following administration of chemotherapy, small amounts of drug leak out of capillaries in the palms of the hands and soles of the feet. The exact pathogenesis of HFS is still unclear. A causal link with the metabolite of 5FU is suspected [1].

Exposure of hands and feet to heat as well as friction increases the amount of drug in the capillaries and increases the amount of drug leakage. This leakage of drug results in redness, tenderness, and possibly peeling of the palms and soles. In general hands are more often affected than feet. The erythema looks like sunburn (see Figure 1). The areas affected can become dry and peel, with numbness or tingling developing. HFS is classified in three grades of severity (see Table 1). In severe cases, the chemotherapy might have to be interrupted or the dose reduced.

**Figure 1: Grade 3 hand–foot syndrome**

Despite encouraging practical experience the use of a uridine cream has not so far been supported by a prospective randomised study. The German and European societies for oncological pharmacy (DGOP, ESOP) call on their members and active oncology pharmacists to test the formulation in practice and to provide more evidence for its efficacy. ESOP has received responses from the Czech Republic and Poland.

### Limited studies have been conducted

A small trial has been conducted in SPSK Hospital No.1 in Poznań, Poland. Approval was obtained from the Polish Bioethics Committee before the trial was started.

Ten women over a period of two months were enrolled in a pilot study. They were aged between 37 and 63 years (average 52.3). They were taking capecitabine five days in a row followed by a 2-week break. This cycle was continuously repeated. The date at which HFS first occurred was different in each patient, but it did not start before the second cycle. For seven of the ten patients the hands and feet were affected, for two patients only the hands and for one patient only the feet were affected (see Figures 2 and 3).

The uridine cream was only given to people who had responded insufficiently to glucocorticoids or greasy creams. All of the patients benefited from the cream; in every case the severity of the HFS got better, stage three went to stage two, etc. Success was measured by photographs and by a questionnaire the patients filled in. They were interviewed about symptoms at the beginning of the treatment and at different times while they were using it (2 days, 1, 2, 4, 6 and 8 weeks after starting treatment).

Table 1: Hand–foot Syndrome is divided into three grades

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Hand–foot syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Painless erythema, dysesthesia, paraesthesia, discomfort that does not disrupt normal activities</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Painful erythema, with swelling (discomfort that affects activities of daily living)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Desquamation, ulceration, blistering, severe pain (severe discomfort, unable to work or perform daily living activities)</td>
</tr>
</tbody>
</table>

Prevention rather than cure is the standard recommendation, there are relatively simple measures to prevent HFS:

- Keep the skin well hydrated with emollient cream or ointment
- Avoid contact with hot water
- Avoid mechanical stress, such as scratching, clapping, handicrafts
- Cold baths or ice packs for the hands and feet 3–4 times a day.
Pharmacies in the Czech Republic had to ask the State Institute of Drug Control for permission to use it for human treatment, because uridine is not on the list of authorised substances. After submitting literature data and the results of a pilot study, the General Teaching Hospital, Prague, was given permission to use it for local administration when HFS was diagnosed. Today the pharmacy prepares uridine cream not only for patients from this hospital, but occasionally for patients from other hospitals too.

Over a 2-year period 84 patients who were treated with fluoropyrimidine-based chemotherapy (mainly capecitabine) were given the 10% uridine cream 2–3 times daily and were monitored, if conventional treatment (steroids, emollient cream) had been ineffective. The number of chemotherapy cycles, grade and site of HFS, time of local uridine administration and the grade of HFS after treatment, were evaluated. Sixteen patients stopped uridine treatment after the first unit pack (100 g). The reason was a change of therapy after tumour progression or change of hospital.

Of the remaining 68 patients, no effect was seen in 23 patients (34%). In 45 patients (66%) the intensity of HFS decreased after 2–4 weeks of local administration, by about 1–2 grades. We recorded whether treatment was stopped or continued while the HFS was treated. One patient with a history of allergies developed atypical small white skin papules. Other local or systemic allergic reactions were not observed.

Case study from the Czech Republic

We usually found that treatment could continue if we treated with uridine cream, because it was so effective. In one case, a young girl developed grade 3 HFS. This would usually mean stopping the treatment but her condition was so serious that she continued with the treatment. Improvement started straight away and it took six weeks for the HFS to clear up. If the treatment can be interrupted HFS symptoms are usually relieved much more quickly (in some cases within days).

Hospital Pharmacy of GTH now uses uridine cream regularly and is going to study the mechanism of action. Ms Irena Netíková reports: “We have received financial support from the Czech Ministry of Health for a 4-year research project The intracellular effect of uridine, and its use for treating palmar-plantar erythrodysesthesia after fluoropyrimidine-based treatment”. ESOP urges other pharmacies to follow their example. The latest formula for the cream and paste using carbopol 974 can be found on the Pharmazeutische Zeitung site [3].

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References

Research and development: a way forward for oncology pharmacy

Oncology pharmacy must develop and improve for the benefit of patients with cancer and society in general.

The aims of a scientific society such as ESOP to foster professionalism and raise standards are fundamental. ESOP's continuing achievements are presented annually at the joint scientific meeting of the society and the German Oncology Pharmacy Society (DGOP). Practice and information must be based on scientific evidence as well as validated experience. Therefore, research and development in oncology pharmacy, as in other medical and pharmaceutical sciences, is essential for further progress.

Research:
- must be of high quality and focused on improving cancer treatment and knowledge and improving the patient’s situation
- must have both pharmaceutical and medical relevance, be clearly formulated, well structured and fully documented
- results should be disseminated to the scientific world and to oncology pharmacy
- should be open to all, and
- relies on expert oncology pharmacists to provide support and supervision.

The oath ‘not to hurt’ is a leading objective.

Delegates from all ESOP countries were asked about research activities in a recent survey. There are only a few sites with ongoing studies within laboratory sciences such as pharmacokinetics and stability and compatibility of cytotoxic drugs. A compelling exception is the pharmacy at Karolinska Hospital in Stockholm, Sweden, where for more than 30 years a department has conducted chemistry and pharmacokinetic studies on cytotoxic drugs in close collaboration with the clinics. Other pharmacies in the university hospitals in Sweden have been able to pursue similar projects. Other highly active centres can be found in Germany and at the Department of Pharmacy and Toxicology at CHU Henri Mondor in Paris, France, headed by Professor Alain Astier, Vice President of ESOP. The CHU Henri Mondor Centre has excellent equipment for analysing cytotoxic drugs at very low concentrations. This centre is also a part of a university institution, the usual setting for these activities.

Other countries are engaged in patient surveys, validation of projects to improve patient support, medical error surveillance and pharmacoeconomic studies. Those surveyed suggested a number of areas in which ESOP should initiate research (see Table 1).

People were generally interested in undertaking R & D in oncology pharmacy providing that resources and time were available. It is a hard and difficult decision that may require a lot of imagination and endeavour to get started. However, results ‘don’t grow on trees’ or in Swedish Du skall inte förvänta att stekta sparvar flyger in i din mun. A scientific project would increase your competence, your professionalism and generate a lot of enjoyment. You should start small - remember advice and support are around the corner. At present there are several oncology research projects with funding from the drug industry, for example, on oral chemotherapy. Often interdisciplinary collaboration is required and this might hamper some progress. However, working together with other healthcare professionals is a challenge that may widen the remit of oncology pharmacy. Local funding and collaboration with patient organisations are other options. Activities are numerous. You could start small by introducing an easy exercise programme for patients with fatigue, monitoring the efficacy of pain relief or improving therapy for emesis following cytotoxic drugs. A multicentre clinical trial is already being planned by ESOP for patients with breast cancer.

In conclusion, R & D is a priority for ESOP. Initiatives are being taken to start and support a variety of projects. Participation will help not only cancer patients and society, but also participants as their competence grows.

Table 1: Areas of research in oncology pharmacy

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of countries interested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability and compatibility of cytotoxic drugs in admixtures</td>
<td>5</td>
</tr>
<tr>
<td>Pharmacokinetics - Pharmacodynamics to improve cytotoxic drug dosing</td>
<td>4</td>
</tr>
<tr>
<td>Clinical evaluation of dose banding</td>
<td>4</td>
</tr>
<tr>
<td>Medical errors</td>
<td>3</td>
</tr>
<tr>
<td>Patient information and counselling</td>
<td>3</td>
</tr>
<tr>
<td>Pharmacoeconomic validation of cytotoxic drug cost</td>
<td>2</td>
</tr>
<tr>
<td>Safe preparation and handling of cytotoxic drugs, oral cytotoxics, guidelines for support therapy, role of pharmacist in the team</td>
<td>1 each</td>
</tr>
</tbody>
</table>

In conclusion, R & D is a priority for ESOP. Initiatives are being taken to start and support a variety of projects. Participation will help not only cancer patients and society, but also participants as their competence grows.

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The role of European oncology pharmacists in patient education in CML treatment — Professor Alain Astier

Drug treatment is constantly being refined and new challenges are posed to pharmacists. How well do we respond to them?

SOP considers dissemination of professional information a significant aspect of oncology pharmacy practice. The aim of this survey was to gain a better understanding of the role of European oncology pharmacists in patient education in chronic myeloid leukaemia (CML) treatment.

The survey was conducted by means of a printed and online survey between January and July 2008. Eleven countries (Poland (21), France (13), Czech Republic (12), Germany (10), Switzerland (5), Hungary (4), Spain (3), Denmark (2), Slovenia (2), Austria (1), UK (1)) replied with a total of 74 valid survey responses. This equals 38% of countries approached but only a small number of total responders, unequally distributed between the different countries. There was a representative balance of age, gender and experience among the responders however.

Fifty-three respondents (76% of valid responses) did not have a specialist qualification in oncology pharmacy, whereas 24% did. Twenty-nine per cent of those who answered had obtained a pharmacy degree, 28% had a masters degree, and 16% a doctorate. Fifteen per cent of the total number of respondents had titles of Doctors and Professors. Sixty per cent were pharmacists and 28% Chief Pharmacists. Twenty-five respondents were members of their hospital’s Formulary/Pharmacy and Therapeutics Committee.

Concerning inpatient malignancies, respondents came into contact most often with patients with colorectal cancer (18% of total responses), then breast cancer (16%), leukaemia (including CML, CLL, AML - 11%), lung cancer (10%) and lymphomas (8%).

Most pharmacists (58% first prescription, 74% further prescriptions) had less than five minutes with a patient, while 51% commented that the amount of time was not related to the form of drug. The point of the survey is that the treatments for CML are oral and therefore adherence of the patient to the treatment becomes a factor and education is important.

Thirty-eight per cent agreed with the statement ‘I have a limited role in educating patients about managing side effects’. Fifteen per cent disagreed, while for 26% the statement did not apply. Thirty-three per cent rated their role in the clinical team as ‘pivotal’ while 27% did not and 22% found the term did not apply. There was a similar spread of responses to questions about communication skills and training. To educate patients in management of their cancer, 30% used printed materials from pharmacy companies, 25% used materials from NGOs and government, 16% produced printed material internally and 11% downloaded materials from the Internet.

CML treatments and guidelines

Surveyed on their familiarity with oral treatments in CML, about a quarter claimed a good knowledge of imatinib (Glivec), while familiarity with dasatinib (Sprycel) and nilotinib (Tasigna) was lower. As many as 56% of the respondents had no knowledge of Tasigna. Of course each drug is not available in every country. Only 6% of respondents were aware of the existence of guidelines for the evaluation of clinical response with CML treatment. The understanding of the main causes of clinical failure with CML treatments scored low as well, with 60% of 66 respondents not knowing what these causes could be. The hospitals of 82% of respondents do not develop guidelines for CML treatment.

Oncology pharmacist involvement with the therapeutic decision process in CML treatment was low. Thirty-six per cent of 61 respondents offered advice on dosage adjustments when they were asked about organ dysfunction, drug interactions or side effects. However only 5% could offer advice about blood levels of imatinib. For Glivec, 56% of 57 respondents were not aware of any guidelines on possible drug interactions. Most (76–80%) hospital oncology pharmacists were not involved in advising on CML treatment.

Comment

This survey shows the difficulty of achieving a uniform level of knowledge and hence treatment for a relatively rare condition. Glivec received marketing authorisation from the EMEA in November 2001 and the new treatment was well publicised. Underlying this is a lack of appreciation of the value of good education for patients. Good material is available in English from Cancerbackup [1] and in English and Spanish from the American Society of Clinical Oncology [2].

An important concern, increasingly underlined by patient advocates, remains the underestimated problem of poor adherence to anticancer treatments, particularly with oral drugs such as tyrosine kinase inhibitors taken for a long period. Pharmacists should improve compliance by carefully managing the side effects: these are made worse by inappropriate food–drug interactions or poor timing of taking the drug. Suitable patient counselling may be helpful.

There is much for ESOP to do in promoting the development of treatment guidelines, continuing education of pharmacists and the role of pharmacists in the management of cancer.

References
1. www.cancerbackup.org.uk/Cancertype/Leukaemichronicmyeloid
2. www.asco.org/patient/Cancer+Types/Leukemia+++Chronic+Myeloid+++CML
A comparison is made of the different approaches being taken to overcome glioblastoma. At this stage, treatment is not yet standard or successful, but at least it is improving.

Glioblastomas rank amongst the most malignant types of tumour in man, although the incidence with three cases per 100,000 population is relatively low. In Germany, 2,500 new cases/year are diagnosed, and of these 50% of patients pass away in the first year. The treatment of choice is where possible radical operation and subsequent radiotherapy of the extended tumour region with a total cumulative dose of 60 Gy in conventional fractionation, i.e. over a period of six weeks. Temozolomide (TMZ), marketed as Temodal in Europe and Temodar in the US, has become the standard treatment in Germany. Chemotherapy is given in parallel, in addition to radiation. The dose during radiotherapy is 75 mg/m² administered daily, including weekends (see Figure 1). The capsules are taken with a little water on an empty stomach in the morning. Sensitive patients will also need an antiemetic after radiotherapy has finished, four to six courses of chemotherapy alone are administered, at 4-week intervals, each for five days in the classical way within five days, 30 x 2 Gy (cumulative dose 60 Gy). In arm A temozolomide was administered at a concentration of 150 mg/m² over six cycles in the classical way within five days, there was then a week’s interval, then repetition with a total of three cycles. Overall survival after six months came to 60% in the TMZ group versus 44% in the procarbazine group, whereby the difference was significant. Six-month PFS was 21% in the TMZ group, 8% in the PCB group (p = 0.008). All in all, with regard to the duration of the relapse-free interval, temozolomide was greatly superior to procarbazine. There was also a slight advantage in the temozolomide group regarding toxicity in reference to severe side effects degrees III and IV, as

Table 1: Haematological toxicity

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Number of patients (%)</th>
<th>Simultaneous TMZ treatment n = 284</th>
<th>Adjuvant TMZ treatment n = 223</th>
<th>Total length of study n = 284</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>7 (2)</td>
<td>11 (5)</td>
<td>20 (7)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 (4)</td>
<td>9 (4)</td>
<td>21 (7)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (3)</td>
<td>24 (11)</td>
<td>33 (12)</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19 (7)</td>
<td>32 (14)</td>
<td>46 (16)</td>
<td></td>
</tr>
</tbody>
</table>

In arm A temozolomide was administered at a concentration of 150 mg/m² over six cycles in the classical way within five days, 150 mg/m² of procarbazine was administered in arm B over 28 days, there was then a week’s interval, then repetition with a total of three cycles. Overall survival after six months came to 60% in the TMZ group versus 44% in the procarbazine group, whereby the difference was significant. Six-month PFS was 21% in the TMZ group, 8% in the PCB group (p = 0.008). All in all, with regard to the duration of the relapse-free interval, temozolomide was greatly superior to procarbazine. There was also a slight advantage in the temozolomide group regarding toxicity in reference to severe side effects degrees III and IV, as
far as nausea and vomiting are concerned. Haematotoxicity was minimally worse in the temozolomide group.

There have been many trials seeking better results by changing temozolomide’s dosing schedule; in particular, trials have been run to administer temozolomide in daily reduced single doses over a period of three weeks. There are trials offering temozolomide on a weekly basis; it was reported at the Trends in Central Nervous System Malignancies Conference 2009, Budapest, Hungary, that classical application according to Stupp produces better results with lower toxicity.

Herrlinger et al. published a study in 2006, in which lomustine, an alkylating agent, was administered in addition to the combination of radio/chemotherapy with temozolomide. The treatment plan comprised radiation therapy with 60 Gy over six weeks of 30 Gy in classical hyperfractionation with two fractions/ day of 1.2 Gy.

Vredenburgh et al. presented their results with reference to bevacizumab and irinotecan in 2007. Two treatment groups were formed; bevacizumab 10 mg/kg body weight and irinotecan 140 mg/m² were administered to the first group, while the same antibody concentration plus 125 mg/m² of irinotecan were given to the other group. The efficacy of irinotecan was increased by giving preliminary anti-epileptic treatment, since irinotecan is a pro-drug, activated during metabolism. CYP3A4 production is promoted in advance by anti-epileptic drugs. Treatment is by IV administration every two weeks over a 6-week cycle until progression. This treatment is standard in our clinic after renewed radiation carried out during the preliminary stages with a cumulative dose of 30 Gy in classical hyperfractionation with two fractions/day of 1.2 Gy.

To compare with traditional chemotherapy, Yung et al. presented a controlled study in 2000, in which temozolomide was tested against procarbazine. This was a randomised multicentre phase II study, in which 225 adult patients with glioblastomas were subjected to chemotherapy when they relapsed after radiotherapy. The primary end point was PFS after six months and tolerance to the therapy. The secondary end point was overall survival as well as the quality of life.

Table 2 surveys the relapse therapy of glioblastoma as well as the corresponding results, which includes all the cases involved in preliminary phase I and phase II studies. Controlled comparisons are completely absent.

Literature can be requested from the authors.

### Table 2: Summary of studies - treatment for relapsed glioblastomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Regime</th>
<th>Genomic Medicine Biorepository (GMB)</th>
<th>Chemo naive patients (%)</th>
<th>Relative Risk RR (%)</th>
<th>PFS-6 6-month progression-free survival</th>
<th>95% CI</th>
<th>Time to progression TTP (weeks)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al. 1999</td>
<td>Beta interferon, menogaril 13-cis-retinoic acid, difluoromethylornithine, carboplatin, fluorouracil, procarbazine</td>
<td>225 n.s.</td>
<td>6</td>
<td>15</td>
<td>10–19</td>
<td></td>
<td>9</td>
<td>8–10</td>
</tr>
<tr>
<td>Kapelle et al. 2001</td>
<td>Procarbazine, vincristine, lomustine</td>
<td>63 68.2</td>
<td>11</td>
<td>29</td>
<td>n.s.</td>
<td>13 n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Fine et al. 2003</td>
<td>BCNU and thalidomide</td>
<td>38 50</td>
<td>24</td>
<td>27</td>
<td>15.9–45.9</td>
<td>14.9</td>
<td>8.3–24.6</td>
<td></td>
</tr>
<tr>
<td>Yung et al. 2000</td>
<td>TMZ (150–200 mg/m² over 5 days, every 28 days)</td>
<td>112 35</td>
<td>5.4</td>
<td>21</td>
<td>13–29</td>
<td>12.4</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Brandes et al. 2003</td>
<td>TMZ (150–200 mg/m² over 5 days, every 28 days)</td>
<td>42 0</td>
<td>19</td>
<td>24</td>
<td>14–42</td>
<td>11.7</td>
<td>9–22</td>
<td></td>
</tr>
<tr>
<td>Groves et al. 2002</td>
<td>TMZ (150–200 mg/m² over 5 days, every 28 days) plus marimastat</td>
<td>44 43</td>
<td>13.6</td>
<td>3.9</td>
<td>24–54</td>
<td>17</td>
<td>13–26</td>
<td></td>
</tr>
<tr>
<td>Jackle et al. 2003</td>
<td>TMZ (150–200 mg/m² over 5 days, every 28 days) plus 13-cis-retinoic acid</td>
<td>40 NR</td>
<td>5</td>
<td>32</td>
<td>21–51</td>
<td>16</td>
<td>9–26</td>
<td></td>
</tr>
<tr>
<td>Brandes et al. 2004</td>
<td>TMZ bd (750–1,000 mg over 5 days) plus cisplatin</td>
<td>50 100</td>
<td>20.4</td>
<td>34</td>
<td>23–50</td>
<td>18.4</td>
<td>13–25.9</td>
<td></td>
</tr>
<tr>
<td>Hau et al.</td>
<td>Pegylated liposomal doxorubicin with/ without tamoxifen</td>
<td>28 58</td>
<td>7.1</td>
<td>7.1</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Rich et al. 2004</td>
<td>Iressa (gefitinib)</td>
<td>53 17</td>
<td>0</td>
<td>13</td>
<td>n.s.</td>
<td>8.1</td>
<td>7.9–9.1</td>
<td></td>
</tr>
<tr>
<td>Friedman et al. 2000</td>
<td>Irinotecan only</td>
<td>48 n.s.</td>
<td>17</td>
<td>n.s.</td>
<td>n.s.</td>
<td>18</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Brandes et al. 2004</td>
<td>BCNU plus irinotecan</td>
<td>42 0</td>
<td>21.4</td>
<td>30.3</td>
<td>18.5–49.7</td>
<td>16.9</td>
<td>11.7–23.5</td>
<td></td>
</tr>
</tbody>
</table>

n.s.: not specified
Bone metastases and treatment by irradiation

Radiation therapy is one of the most important tools in the treatment of bone metastases. Using the evidence base of modern, recently published clinical trials, it is possible to propose treatment with good scientific evidence. It must be used as part of a global strategy and decisions on its use must be made in multidisciplinary meetings.

A meta-analysis by Wu et al. [1] evaluated all trials of bone irradiation for treatment of metastases. They were amalgamated in three categories:
- Single fraction: 4 Gy vs. 8 Gy
- Single fraction versus multiple fractions
- Different modalities of fractionation: 15/20 Gy vs. 24/30 Gy

The primary outcomes of interest were complete and overall pain relief. But the response was analysed according to different criteria: the most important effects were complete response or the global response.

Single fraction 8 Gy dosing seems to have been the most effective but there was no difference in complete response. No difference was demonstrated, in complete response, in the trials comparing single versus multiple fractions (34.4% vs. 32.3% (p = 0.5). Nevertheless if the global response was considered, giving the radiation as a single dose was more effective (62.1% vs. 58.7%; p = 0.04; RR = 1.05). No dose-response effects were demonstrated when looking at the different schemes, but re-irradiation was more frequent with low doses and fractures were more frequent with single doses than with multiple fraction treatments.

Finally the length of the response varied from 11 to 24 weeks while the acute tolerance was equivalent in all trials.

With these results in mind, some recommendations can be suggested:
- If the analgesic effect is the principal objective for a single metastasis with no complications, or if there are just a few metastases, the best treatment is treatment in one fraction.
- In the opposite situation, or if the objective is different, the choice can be adapted to the situation. If there is a risk of a fracture, or a significant mass around the bone metastases, or if there is spinal compression, multiple fraction schemes must be used.
- Finally the benefit of highly fractionated doses was not demonstrated even in patients with a good prognosis (see Table 1 and Figure 1).

The results of the recently published RTOG 97-14 trial [2] demonstrated that, at three months, there is an equivalence in period of response between 8 Gy/1 fraction (arm A) and 30 Gy/10 fractions (arm B). Eight hundred and ninety-eight patients were randomised, 288 were analysed in arm A and 285 in arm B. The median survival was 9.1 vs. 9.5 months; the acute tolerance (grade 2 and 3) was 10% vs. 17% (p = 0.002). The late tolerance (grade 2 and 3) was equivalent in the two arms. The risk of fracture was 5% vs. 4% and from the opposite

Table 1: Factors that can modify the strategy for radiation of bone metastases

<table>
<thead>
<tr>
<th>Reasons to choose multiple fraction irradiation</th>
<th>Reasons to choose monofraction irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimises the risk of painful relapse</td>
<td>Evidence: more effective</td>
</tr>
<tr>
<td>Minimises the risk of spinal compression</td>
<td>No survival difference against pain</td>
</tr>
<tr>
<td>Minimises the number of re-irradiation sessions</td>
<td>Choice of the patient</td>
</tr>
<tr>
<td>A common practice</td>
<td>Well-educated physician</td>
</tr>
<tr>
<td>Less burden on long bones</td>
<td>Low performance status</td>
</tr>
<tr>
<td>First metastases</td>
<td>Small number of treatments</td>
</tr>
<tr>
<td>Less dangerous for the spinal cord, brain</td>
<td>Patient lives at a distance</td>
</tr>
<tr>
<td>Young (age &lt;40 yrs)</td>
<td>Workflow of the department</td>
</tr>
<tr>
<td>Lytic metastasis</td>
<td>Older patients</td>
</tr>
</tbody>
</table>

Figure 1: The dose delivered to a tumour in the cervical spine

Radiation of a vertebral metastasis with three beams: one anterior, one oblique posterior right and one oblique posterior left. Red: soft tissue extension of the bone metastases; Blue: Planning target volume (PTV); Green: Isodose 95% (all tissues inside received at least 95% of the prescribed dose).
perspective re-irradiation was more frequent in arm A (18% vs.
9%, p < 0.01). Only patients with breast and prostate cancer
were included in this trial. The pain was evaluated only in 573
patients at three months and 160 patients had died or were too
tired to answer the questionnaire.

Van der Linden et al. [3] analysed the patients who survived
one year after inclusion in a prospective trial which evaluated
irradiation with one fraction versus 24 Gy in six fractions,
1,157 patients were included; 320 patients survived. In 63% of
patients the primary tumour was breast cancer, 24% prostate
cancer, 8% lung cancer and 5% different localisations. In the
one fraction arm 163 patients were alive vs. 157. A global
response to pain was obtained in 87% vs. 85%, which was
complete in 62% vs. 48% of subjects. The median survival was
35 and 42 weeks respectively. No difference could be shown in
the evolution of the pain during the first year, nor did the
differing histology of the primary tumour appear to correlate
with the effectiveness of the treatment. The analysis of sur-
vival in the 1,157 patients showed that the survival differed
significantly for breast cancer, prostate cancer and the other
tumours or lung cancer. Fifty percent of the patients were alive
at 18, 12 and six months, respectively.

Several prognostic factors were demonstrated regarding the
efficacy of the treatment. These factors were Karnofsky score
>80, the number of bone metastases (single or multiple), vis-
ceraler metastases, treatment with morphine, pain score 8–10 on
the EVA scale and finally systemic treatment. (The Karnofsky
index gives clinical estimate of a patient’s physical state,
performance, and prognosis after a therapeutic procedure on a
scale 0–100. EVA equates maximum pain to 10.)

Finally, recent trials with sufficient power have shown equiv-
alance between irradiation in one fraction and irradiation in five
to six fractions. But in practice, what can be offered to
the patient? How does practice vary in different countries and
finally what do patients choose? Lievens et al. studied prac-
tice in different countries and institutions classified accord-
ting to the number of patients treated per year [4]. Treatment
in multiple fractions is generally used in Canada, Europe,
New Zealand and USA. Within this there is a large hetero-
geney of practices. These justify the therapeutic choices
presented in Table 1.

Patient preferences were evaluated by Shakespeare et al. [5].
After being informed of the advantages and the risks of two
strategies (8 Gy/1 fraction and 24 Gy in six fractions), 62
patients were included. Eighty-five percent of the population
chose the fractionated treatment. Their reasons for this were
firstly the risk of re-irradiation and secondly bone fracture.

The other 15% of patients based their choice on the cost and
the convenience of only one treatment. No objective criteria
were found to distinguish the two groups. But 84% of
patients were very positive about being involved in the treat-
ment decision.

**Conclusion**

Treatment of bone metastases is an important option but is fre-
quently used belatedly. In the light of modern trials, it should
be considered earlier, as active treatment, but trials have not
yet been large enough to give firm indications of treatment
options. The populations included in these trials are usually a
mixture of patients with metastases from breast, prostate and
lung cancer. Only in one trial did the population consist of
patients with metastases solely from breast tumours [6]. The
impact of new medical treatments such as bisphosphonates has
also not yet been evaluated in published trials. Finally, I would
like to call for trials of irradiation associated with new drugs
and trials of metabolic irradiation.

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**References**

fractionation radiotherapy trials for the palliation of painful

2. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial
of short versus long-course radiotherapy for palliation of

3. Van der Linden YM, Steenland E, van Houwelingen HC, et
al. Patients with a favourable prognosis are equally palliat-
ed with single and multiple fraction radiotherapy: results on
survival in the Dutch Bone Metastasis Study. Radiother
Oncol. 2006;78(3):245-53.

4. Lievens Y, Kesteloot K, Rijnders A, et al. Differences in pal-
liative radiotherapy for bone metastases within Western

radiotherapy fractionation schedule in the palliation of painful

6. Rasmusson B, Vejborg I, Jensen AB, et al. Irradiation of
bone metastases in breast cancer patients: a randomized
study with 1 year follow-up. Radiother Oncol. 1995;34
(3):179-84.
Erythropoiesis-stimulating agents (ESAs) are an established, effective treatment for anaemia in patients with cancer and chemotherapy-induced anaemia [1-3]. In 2007, the European Commission gave final marketing approval for Retacrit® (epoetin zeta), a biosimilar ESA licensed for the treatment of anaemia associated with either chemotherapy (administered subcutaneously) or chronic renal failure (CRF; administered intravenously) [4]. Retacrit was approved on the basis of strong, compelling safety and efficacy data, and compliance with extensive European clinical, non-clinical and quality guidelines. New published data from Tzekova et al. [5] support the safety, tolerability and efficacy of subcutaneously administered Retacrit in patients with chemotherapy-induced anaemia.

Retacrit phase III data

The study by Tzekova et al. presents data from an open-label, international, multiple-dose phase III study of Retacrit for the treatment of anaemia in 216 patients with solid tumour(s) or non-myeloid haematological malignancies receiving chemotherapy and at risk of transfusion. Retacrit steadily improved mean haemoglobin (Hb) levels over 12 weeks of treatment, with a significant overall increase of 1.8 g/dL (p ≤ 0.0001; Figure 1). Within the first 8 weeks of treatment, 81.5% of patients had achieved ≥1 g/dL increase in Hb and 70.8% of patients had achieved ≥2 g/dL. These results are similar to previous reports for other epoetins [1]. A total of 81% of patients remained transfusion independent throughout the 12-week study period and quality of life improved as assessed by the Zubrod performance score.

The safety of Retacrit compared favourably with data from other studies of epoetin alfa and epoetin beta as well as darbepoetin. Within the first 12 weeks of Retacrit treatment, 4.2% of patients experienced a clinically significant thrombotic event, which was similar to the median incidence rate of 4.5% (range 0-30%) from a meta-analysis of 6,769 patients from 35 ESA trials [6]. Adverse events throughout the study were consistent with the underlying disease state and chemotherapy treatment, and were comparable with those reported in previous studies of epoetin alfa and epoetin beta in similar patient populations [1, 3].

Summary

Comparable efficacy and safety to epoetin alfa has already been demonstrated for Retacrit in the treatment of anaemia in patients with CRF [7-9]. Data from this recently published oncology study demonstrate that epoetin zeta is a well-tolerated and effective treatment for anaemia in patients with chemotherapy-induced anaemia who are at risk of transfusion, and are consistent with data generated in other epoetin studies of similar design [1, 3].

Hospira is a global, independent, specialty pharmaceutical company based near Chicago, Illinois, USA. It has 70 years’ service to health care and state-of-the-art technology, and is already the European leader in supplying generic injectable agents.

Contact

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Email: retacrit@caudex.com

References

Re-escalation of sunitinib dose following dose reduction for thrombocytopenia

We report the case of a patient with metastatic renal cell carcinoma who achieved long-term benefit with the tyrosine kinase inhibitor, sunitinib. After initiation, sunitinib dose was reduced due to thrombocytopenia. Dosing was re-escalated after progression, and stable disease >12 months achieved.

Initial treatment
A 59-year-old male patient presented with haematuria in June 1999 and was subsequently diagnosed with a right renal carcinoma, with no evidence of metastatic disease. In March 2000, a right nephrectomy was performed and subsequent histology was consistent with renal cell carcinoma (adenocarcinoma). During routine follow-up in December 2001, computed tomography (CT) scan showed two mediastinal lesions, which were resected laparoscopically. Interoperatively, these lesions were noted to be adherent to the pulmonary artery, therefore, surgery was followed by adjuvant radiotherapy for five weeks.

In May 2005, two further metastatic lesions were surgically removed: a single para-aortic lymph node and a supra-renal nodule (found not to be adrenal on pathology). Treatment with interferon-alpha (IFN-α), escalating to 9 MU three times weekly, was initiated in April 2006 for multiple intra-abdominal nodules. However, after three months of treatment, disease progression was observed on CT scan, with a 50% increase in nodal disease. Therefore, IFN-α was discontinued and the patient was referred to our institution for consideration of treatment with sunitinib via an expanded-access programme [1].

Treatment for metastatic disease
It was noted that the patient had a medical history of hypertension, managed with three antihypertensive agents (diltiazem, bendroflumethiazide and valsartan) and was an ex-smoker of 15 years. The patient presented with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0. Blood pressure was elevated at 169/105 mmHg. Baseline full blood count was normal and analysis of serum electrolytes revealed mild renal impairment. A CT scan prior to treatment showed retroperitoneal lymphadenopathy and a 1 cm peritoneal deposit.

The therapeutic goal for this patient with good performance status was to prolong survival by maximising efficacy. An additional aim was to maintain the patient’s performance status and quality of life. It was also important to ensure that the patient’s concomitant hypertension was effectively controlled during treatment.

Sunitinib was initiated in August 2006 for metastatic renal cell carcinoma (mRCC) at the recommended dose of 50 mg once daily (four weeks on treatment followed by two weeks off treatment; Schedule 4/2). After the first four weeks of treatment the patient experienced a number of drug-related side effects, including grade 3 hand–foot syndrome (HFS) with erythema, blistering and soreness of the hands and feet (see Figure 1). Other side effects included fatigue, flushing, mucositis, stomatitis and diarrhoea (all grade 1). Grade 1 alopecia, areas of hair depigmentation, and a yellowish tinge to skin were also noted.

All these symptoms improved considerably during the 2-week off treatment period. HFS was treated mainly with emollient creams and the avoidance of harsh detergents and hot water, where possible. Diarrhoea, when it occurred, responded well to treatment with loperamide. Mucositis was managed with advice regarding oral hygiene and the regular use of chlorhexidine mouthwash. The patient kept a meticulous diary throughout treatment and all noted side effects of treatment improved after the 2-week off treatment period. The patient was given advice on managing fatigue. Grade 1 alopecia, hair depigmentation, and skin discolouration do not require medical intervention. The patient was counselled ahead of treatment commencement about the possible occurrence of these changes.

After two cycles of sunitinib treatment, widespread bruising (ecchymoses) was observed on the patient’s torso. Grade 3 thrombocytopenia was reported (platelet count of 37 x 10^9/L). There was no evidence of active bleeding and so this was managed conservatively. At this time, a CT scan showed a significant treatment response (not amounting to a partial response)
with respect to lymphadenopathy in the pre- and para-aortic areas (see Figure 2). The patient’s dose of sunitinib was reduced to 37.5 mg once daily (Schedule 4/2). Within two weeks the patient’s platelet count returned to normal (153 x 10^9/L). HFS also improved to grade 2 and diarrhoea, mucositis and fatigue continued, but they were manageable with standard medical intervention as described above and in the discussion.

After five cycles of sunitinib treatment, subclinical hypothyroidism (thyroid-stimulating hormone [TSH] 83.76 mU/L and free T4 < 5.1 pmol/L) was observed and treatment with thyroxine 100 μg was commenced. The patient’s response continued to be monitored by CT scans with alternate cycles. After four cycles of treatment stable disease was observed and after six cycles a further reduction in the retroperitoneal lymph nodes was demonstrated.

In September 2007, after 10 cycles of sunitinib treatment, CT showed a measurable increase in the retroperitoneal lymph nodes and the decision was taken to re-escalate sunitinib to 50 mg once daily (Schedule 4/2). The platelet count remained stable and within the normal reference range. HFS and diarrhoea worsened briefly but returned to baseline (grade 1 or 2) within two cycles. HFS and diarrhoea were managed as previously described.

After three months, a CT scan showed stable disease with no further increase in the size of the retroperitoneal lymphadenopathy. During the subsequent 12 months the patient experienced slow, small volume disease progression (stable by Response Evaluation Criteria in Solid Tumours [RECIST] [2]) seen on sequential CT scans. In early 2009, the patient exhibited deterioration in ECOG PS and clinical signs of disease progression and was admitted to his local hospital with a lower respiratory chest infection. Sunitinib was therefore discontinued at this point. The patient is currently being treated symptomatically in the community, with an emphasis on palliative care. For the majority of time that the patient was receiving treatment with sunitinib he had a good quality of life and continued to work in his chosen profession whilst on treatment.

### Discussion

Sunitinib is approved internationally for the treatment of advanced or metastatic renal cell carcinoma with a recommended starting dose of 50 mg once daily on Schedule 4/2. In the case reported, thrombocytopenia associated with sunitinib treatment resulted in a temporary dose reduction to sunitinib 37.5 mg once daily (Schedule 4/2), in line with recommendations in the product labelling [3]. Following disease progression, the patient was successfully dose re-escalated to sunitinib 50 mg once daily (Schedule 4/2) which resulted in stabilisation of disease for >12 months.

Across clinical trials, sunitinib has demonstrated a consistent adverse event profile, with the majority of events grade 1–2 in severity. As such, sunitinib is associated with a distinct and predictable profile of adverse events [4]. In the pivotal phase III trial assessing first-line treatment with sunitinib in patients with mRCC, diarrhoea, fatigue and nausea were the most common adverse events observed during sunitinib treatment [5]. In general, adverse events improved during the 2-week off treatment period. Therapy management by prompt and effective treatment of adverse events may help to reduce their impact on patients. The majority of adverse events associated with sunitinib are manageable with standard medical intervention; however, for some adverse events temporary cessation of drug or dose reduction may be necessary. Within the phase III study, 38% of patients on sunitinib had a dose interruption and 32% underwent a dose reduction.
In this case report, adverse events were similar to those observed in the phase III trial. Hypertension is a recognised side effect of several targeted agents, and blood pressure monitoring is recommended for every clinic visit [3, 6–8]. Treatment with antihypertensive agents may prove necessary and these agents can generally be combined with sunitinib without interactions. Interestingly, in this case the patient was already suffering from elevated blood pressure prior to initiation of therapy and there was no worsening of this during sunitinib treatment. HFS is also well recognised, with patients describing erythema of the palms of hands and soles of feet, dry skin, desquamation, hyperkeratosis and increased skin sensitivity [9]. This particular side effect is treatable and responds best if detected early. Typical interventions to mitigate this problem include the liberal use of emollients, avoidance of irritants including hot water and bright sunlight, use of cotton socks and gloves and well-fitting footwear. Diarrhoea generally responds well to anti-diarrhoeal agents such as loperamide. Stomatitis may be treated with appropriate oral care [10]. Management of fatigue first requires exclusion of any reversible contributing factors such as anaemia and hypothyroidism. Following this, advice is given to patients regarding energy saving, accepting help from others, taking regular exercise and maintaining regular sleeping habits. Help with time planning is also offered, in particular taking advantage of the 2-week break off treatment when symptoms such as fatigue often improve.

In the phase III trial, grade 3 thrombocytopenia was observed in 8% of patients receiving sunitinib; other haematological abnormalities were also seen, including neutropenia and anaemia. Interestingly, in this case, re-escalation of the sunitinib dose from 37.5 mg once daily to 50 mg once daily did not result in reappearance of previously documented thrombocytopenia. This may be explained by the pharmacological phenomenon of tachyphylaxis where a decreasing response to a drug given over a period of time is observed (with reference to toxicity in this case). Thrombocytopenia is usually managed conservatively with either time off sunitinib or a dose reduction in the drug. Further measures such as platelet transfusion are not usually required.

When considering dose reductions, it is important to note that exposure-response models have demonstrated that there is a correlation between higher sunitinib exposure and improved progression-free survival and overall survival [11]. In this case, re-escalation of the sunitinib dose following disease progression resulted in stabilisation of disease. This demonstrates the importance of using the optimal sunitinib dose, and maintaining therapy while efficacy is observed, to achieve maximum clinical benefit.

In conclusion, this case demonstrates that a patient can achieve long-term benefit with sunitinib through appropriate therapy management by treatment of adverse events and sunitinib dose modification where necessary. The dose of sunitinib can be re-escalated to maintain clinical benefit.
Cancer is a common disease. The probability that a person will be diagnosed with cancer in his or her life time is approximately one in two for men and one in three for women. No doubt, past investment in cancer research has led to significant advances in preventing, detecting and treating the disease. In the US the cancer death rate decreased by an average of 1.1% a year from 1993 to 2002 and by an average of 1.8% from 2002 to 2005. The 5-year relative survival rate for all cancers diagnosed between 1996 and 2004 was 66%, up from 50% between 1975 and 1977. After years of robust investment funding for cancer research in the US there are today more than 11 million cancer survivors in the US – up from just three million in the 1970s – and cancer death rates have dropped 18% among men and 10% among women since the early 1990s.

Robust investment in budgets of the National Institutes of Health and National Cancer Institute helps:

• **tailor treatments in elderly cancer patients** (two out of three cancer patients are older than 65 years, have decreased organ function and suffer simultaneously from significant comorbidity. Thus, it is important to personalise standardised cancer care) and

• **identify patients who are most likely to benefit** from particular treatments, while avoiding undesired treatment effects and costs in the others.

Many results of this public funding of cancer research are published annually at the American Society of Clinical Oncology (ASCO) meeting. Unfortunately, in most parts of Europe we do not give the same support to funding of cancer research. In comparison to the US the survival rate of cancer patients in Europe is significantly lower. We do not even know how low in some parts of Europe. This is why we should pay attention to the results presented at the ASCO meeting.

### Lung cancer

**Pemetrexed as maintenance therapy** extends survival. A phase III study reports (663 patients) that maintenance therapy with pemetrexed (Alimta) improves survival (13.4 months versus 10.6 months) in non-squamous forms of advanced non-small cell lung cancer. Patients with the squamous subtype do not benefit. Pemetrexed is currently approved as a first-line treatment for advanced or metastatic non-squamous non-small cell lung cancer in combination with cisplatin and as a single agent in patients with recurrent disease (Belani et al. Abstract # CRA 8000).

**Novel therapy that targets two receptors** benefits patients with advanced lung cancer. A phase III trial (1,391 patients) demonstrates that vandetanib (Zactima), a novel drug that targets two key receptors associated with lung cancer growth, improves progression-free survival in patients with advanced non-small cell lung cancer (Herbst et al. Abstract # CRA8003).

**Oestrogens and progestins linked to increased risk of death** in women with lung cancer who are having menopausal hormone therapy. A secondary analysis from the Women’s Health Initiative reports that use of hormone therapy with oestrogens plus progestin increases the risk of dying from non-small cell lung cancer for women with the disease (Chlebowski et al. Abstract # CRA1500).

### Gastrointestinal cancers

**Octreotide LAR significantly prolongs time to progression** in metastatic neuroendocrine mid-gut tumours. The phase III trial (89 patients) finds that the IM injection of 30 mg octreotide (Sandostatin) every four weeks prolonged the median time to progression to 14.3 months compared to six months (placebo). The median overall survival is at present longer than 77.4 months (placebo 73.7 months).

First-ever data shows **bevacizumab as adjuvant therapy of no benefit** in UICC stage II and III colon cancer. A phase III trial (2,720 patients) finds that adding the targeted therapy bevacizumab Avastin to standard adjuvant FOLFOX6 chemotherapy did not improve disease-free survival for patients with locally advanced colon cancer (Wolmark et al. Abstract # LBA4).
Adjuvant treatments for pancreatic cancer compared. A phase III study comparing the adjuvant treatments most commonly used for pancreatic cancer in Europe and the US (gemcitabine and 5FU/Folinic acid, respectively) found that there is no difference in survival between the two regimens, though gemcitabine was associated with fewer side effects (Neoptolemos et al. Abstract # LBA4505).

The current standard is supported for anal cancer. The largest study to date confirms continuous radiation combined with 5FU and mitomycin-C chemotherapy. A phase III trial (940 patients) finds that this current standard treatment for anal cancer should not be changed and that maintenance therapy (cisplatin and 5FU) after initial treatment is not effective (James et al. Abstract # LBA4009).

Local tumour control is not improved by adding oxaliplatin (Eloxatin) to preoperative chemoradiotherapy for locally advanced rectal cancer. A preliminary analysis suggests the treatment may reduce distant metastases, however. In this phase III trial, 747 patients with locally advanced rectal cancer were randomised to receive standard preoperative chemoradiotherapy (50.4 Gy in 28 daily fractions and 5FU 225 mg/m²/day) or the standard plus oxaliplatin (+ weekly 60 mg/m² x 6) (Aschele et al. Abstract # CRA4008).

Trastuzumab improves survival for patients with HER2-positive locally advanced, recurrent, or metastatic gastric cancer. Among patients with gastric cancer tumours that express high levels of the HER2 protein, those who received trastuzumab (Herceptin) plus chemotherapy (5FU or capecitabine and cisplatin) lived significantly longer than patients who received standard chemotherapy alone, with a 26% reduction in the risk of death. In this large phase III trial (3,807 patients) median overall survival was 13.8 months in the trastuzumab group versus 11.1 months in the chemotherapy-only group (Van Cutsem et al. Abstract # LBA4509).

Breast and gynaecological cancers

New class of targeted therapy: PARP inhibitors. Two new studies reported results on the effect of so-called PARP (Poly (ADP-Ribose) Polymerase) inhibitors on traditionally difficult-to-treat breast cancer, what is known as ‘triple negative’ (ER, PR, HER2 negative) breast cancer.

Cancer cells use the PARP enzyme to repair DNA damage, including the damage inflicted by chemotherapy drugs. The first study, a randomised phase II study (86 patients) shows that women with metastatic triple-negative breast cancer who received the investigational PARP inhibitor BSI-201 in combination with conventional chemotherapy (gemcitabine plus carboplatin) lived significantly longer and experienced significantly better progression-free survival than women who received standard chemotherapy alone. Approximately 62% of patients receiving BSI-201 showed clinical benefit compared with 21% in the chemotherapy-only group. The overall response rate to treatment with the drug combination containing BSI-201 was significantly greater (48%) than in the group receiving only chemotherapy (16%). Women who received BSI-201 had a median survival of 9.2 months compared with 5.7 months in women who received chemotherapy alone (O’Shaughnessy et al. Abstract # P3).

The other study, a small phase II trial on 54 patients with BRCA-deficient breast cancer, showed that PARP inhibitor olaparib induces tumour response as single agent. Tumours that arise in patients with BRCA mutations have a defect in their ability to repair DNA. By adding olaparib, the tumour cells are deprived of another DNA repair mechanism. It is thought that this added inhibition of DNA repair with olaparib then leads to cancer cell death. In this study, 40% of the patients responded to olaparib. Olaparib was well tolerated, with the common side effects being mild fatigue, nausea and vomiting (Tutt et al. Abstract # CRA501).

Adding gemcitabine to chemoradiation improves survival in women with locally advanced cervical cancer. A phase III multicentre study (259 patients) showed that adding gemcitabine (125 mg/m² weekly x 6 doses with concurrent radiation and then two adjuvant 21-day cycles at day 1 and 8 at a dose of 1,000 mg/m²) to a regimen that includes cisplatin (50 mg/m² on day 1), radiation (50.4 Gy in 28 fractions) and brachytherapy (30–35 Gy) extends overall survival among women with locally advanced cervical cancer. Brachytherapy is radiation treatment given by placing radioactive material directly in or near the target, which is often a tumour.

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Reference