Allergic reactions to oxaliplatin therapy – an overview
Improving the care of anorexia-cachexia patients
Cisplatin combined with other drugs - how drugs affect one another and the patient

Models of tumourigenesis and their relevance for tumour pharmacology
Pharmacoeconomic trends in Germany: searching for evidence?
Complementary and alternative medicine in cancer patients

The new era of trabectedin in soft tissue sarcomas

Important advances in haematology for cytotoxic drugs
Standardised labels for cytotoxics

Tumour lysis syndrome – prevention and treatment
Improving the care of anorexia-cachexia patients
Allergic reactions to oxaliplatin therapy – an overview

Vertical shock tests with safety packaging materials for cytotoxic drugs

Important advances in haematology
ASCO 2008 congress: many new drugs against advanced cancer

Positron emission tomography and its application to clinical oncology
Clinical case study: unexpected toxicities in colorectal cancer treatment

National News
ESOP News
Comment
Meeting Report
Klaus Meier appointed to the board of ECCO

A landmark event occurred on 14 January 2008 when Klaus Meier, President and founder of the European Society of Oncology Pharmacy (ESOP) in 2000, was invited to join the board of ECCO, the European CanCer Organisation. This body was born in the early 1980s, when a few visionaries working in European oncology laid the foundations of the Federation of European Cancer Societies (FECS) at a time when multidisciplinarity in cancer care – the idea that tackling cancer was a team effort that required a coordinated approach – was a relatively new concept. Twenty-five years later, multidisciplinarity is accepted everywhere as being the best way to treat cancer.

Last year FECS changed its name and restructured to respond better to the needs of its member organisations and serve the interests of all stakeholders in oncology Europe-wide. ECCO was officially announced at the European Cancer Conference in Barcelona in September 2007, and through its members, represents the interests of over 45,000 professionals in oncology. EJOP interviewed Mr Meier about his appointment.

EJOP: Congratulations! What is the significance to ESOP of your appointment?
Klaus Meier: This gives ESOP a higher profile: more work to do and more opportunities. It is the first time a pharmacist has sat on this main medical board. We can now demonstrate the relevance of oncology pharmacy at a European level, while taking up this challenge individually in our daily work.

EJOP: ESOP is clearly well regarded. How has it achieved recognition?
Klaus Meier: ESOP affiliated with FECS in 2003. Since then we have regularly supported the annual conference. We have distributed 4,000 copies of the quality standard we have developed in many languages. Last year in Barcelona, the 3-hour ESOP symposium attended by 200 people was a great success. Every presentation featured a MD side by side with a hospital pharmacist. This made a big impression.

EJOP: Where does oncology pharmacy go from here?
Klaus Meier: I do not think Europe is necessarily going to follow the same model as the US. We are lagging five years behind in introducing elements of clinical practice into university courses. Each patient’s drug treatment and reaction to it encompasses several factors, such as side effects, interactions, stability issues, etc. We have to bring our theoretical knowledge closer to the patient. A company can produce a summary of product characteristics, but how it applies to each patient is different for each individual. Every person is unique, but as a patient gets older - and many cancer patients are older - their previous medical history is more divergent, their present response is more divergent, and for example the drugs they used to take may no longer be appropriate for their current situation. Doctors do not always see this.

So closer contact is not only the best way to work with doctors, but also with patients. If we in hospital can develop our work in this way, we will in turn assist community pharmacists in looking after patients in the best way, a challenge to which they will increasingly rise as home-based treatment with orally administered drugs becomes more established.

EJOP: What do you see as your role on the Board?
Klaus Meier: I want to give the point of view of pharmacists the impact it deserves. This requires a listening role - I listen carefully to what physicians want and need, and reflect it carefully to pharmacists. Generally speaking, I find that pharmacists are scientists, while doctors are pragmatists. So while we can describe from a theoretical point of view, what will happen in the majority of cases, doctors will be most interested in what actually happens to the 10% or so of patients who do not respond in a typical way, but present individual and real problems. In my opinion, patients are best served when these two perspectives can work together. Then we get the best of both the theoretical and practical points of view.

EJOP: How do you have time to do everything? Please tell readers a little about yourself.
Klaus Meier: I am married, with two teenage daughters. At the moment the reorganisation of the German education system is having an effect on our family, as I’m sure it is on many!

Having studied theology and biblical languages, I was at one time asked to start a drama group with the youth at my church. I chose scenarios that fitted the characters of the young people - I asked them to play characters similar to themselves. It was a great success - everyone said, “What great acting talent you have discovered”. This taught me how to use the same approach in my professional life. If you give people the feeling they are doing well, they respond. I am now blessed with great support from colleagues all over not only Germany, but Europe.
National News

A cytotoxic preparation network in Denmark

The Danish hospital pharmacy cytotoxic preparation network was formed in 2002. The purpose of the network was to create a forum for pharmaceutical staff working with preparation of cytotoxics throughout Denmark and through collaboration to standardise the conditions and quality of the preparation work. The network has become a great success. Over the years the network has kept its focus but also developed subgroups working with special areas:

- Contamination group. The group works with the different topics on safe handling (equipment, devices, dressing, etc.) but also with contamination tests.
- Basic data. This group works by gathering chemical data on the different cytotoxics to make guidelines for the shelf life of prepared doses. The data can also be used in combination with computer systems.

A “Good Practice Standard” for cytotoxic preparation in Danish hospital pharmacies was developed in 2006 as a result of collaboration between the Danish Society of Hospital Pharmacy Managers (DSS) and the network. This standard contains all the most important guidelines for safe handling and compliance with GMP.

Eva Honoré, MSc Pharm, Rigshospitalet, eva.honore@rh.regionh.dk

Polish-German conference on oncology pharmacy

Seventy oncology pharmacists met on 16-17 May 2008 in Frankfurt am Oder for their annual Oncology Pharmacy Conference. The theme “Theory for Practice” resulted in a two-part programme. Speakers of international repute lectured on the theory day, which was followed by a workshop titled “From case to case – how to create and develop reviews of clinical cases from a pharmaceutical point of view”.

Professor Thomas Kichler raised measuring the quality of life of oncology patients, a goal second only to prolonging the survival time. Today we are able to measure health-related quality of life scientifically. Patients with malignant diseases not only ask about their chances of survival, but also about their quality of life. We may present and compare the impact of disease and therapy on the patient – to allow true informed consent. This will only be possible when measurement of quality of life becomes part of international clinical trials.

Professor Piotr Smolewski, an eminent specialist, discussed programmed cell death and concluded that apoptosis-regulating mechanisms are very promising targets for neoplastic treatment. In future he predicted that as the majority of cytostatics act by inducing apoptosis there will be a high possibility of increasing efficacy by combining these agents with others that inhibit the expression of anti-apoptotic proteins. Selective biological anti-tumour agents are emerging as the search continues.

An update on monoclonal antibodies, prevention of fungal infections and presentation of an interdisciplinary information chart completed the lectures. During the workshop, groups of participants examined real oncology patient cases to evaluate the treatment given and to propose improvements to the therapy justifiable from the pharmaceutical point of view.

This successful conference generated a hard-working and friendly atmosphere. Just look at the group photo! The next conference is already planned for April 2009 in Dresden.

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Models of tumourigenesis and their relevance for tumour pharmacology

Understanding the complex interplay between tumour biology and tumour pharmacology is the most promising approach to implement novel and rationally designed pharmacologic concepts. The current models of tumourigenesis are an indispensable impetus to this learning process.

Our ways of treating cancer are greatly influenced by our current understanding of the nature of the disease itself. As the mechanisms underlying disorders are more and more unravelled, treatment strategies have been adapted at increasing speed in the last decade. In this article, the paradigm of colorectal cancer will be used to illustrate the impact of tumour models on therapeutic approaches. "Knowing the enemy" is helping us develop pharmaceutical agents to cure cancer or control the disease (at least temporarily).

Pathologists noticed long before any other discipline that colorectal tumourigenesis often follows a sequential scheme - the colorectal adenoma-carcinoma sequence. The stages observed were the transition from normal mucosa to aberrant crypt foci as the first identifiable lesion, followed by progression to an adenoma, a carcinoma in situ, and to an overt carcinoma. This process is estimated to occur within 15 to 20 years, leaving enough time for diagnostic and therapeutic interventions. It was the merit of Fearon and Vogelstein to link the observed pathologic phenotype to accumulating genetic aberrations [1]. These tumour-driving mutations activate the oncogenes APC, KRAS, p53, and TGF-β type II while at the same time inactivating tumour suppressor genes. This escalation is sometimes overlaid with microsatellite instability in some tumour subtypes. Although this model was extremely stimulating for tumour biology, it was hardly translated into clinical benefit at the beginning. Most of the frequently observed mutations including KRAS or p53 have little predictive value for the therapy with fluorouracil [2]. The exception is probably microsatellite instability, which correlates with higher response rates and overall survival in locally advanced and advanced colon tumours. Possible explanations are that tumours of the breast and the colon usually show an average number of 90 mutations, of which approximately 10% are considered tumour-driving events [3].

The ongoing search for novel models led from genetic to epigenetic events. It was observed that the overall cancer genome is hypomethylated at the promoter sites, but hypermethylated in specific regions. The associated silencing of genes covers very sensitive cellular functions such as cell cycle regulation, DNA repair, signal transduction, rebuilding of the chromatin structure, invasion, and apoptosis. The synthesis of genetics and epigenetics led eventually to the epigenetic progenitor model of cancer proposed by Andrew Feinberg in 2006 [4]. He proposed an integrative view, that a combination of mechanisms results in cellular deregulation, which accelerates tumourigenesis. In this context, our group has recently shown that in parallel to the progression of the adenoma-carcinoma sequence the DNA-methyltransferases responsible for epigenetic aberrations are constantly increasing throughout the process [5]. It is thought that 5-azacytidine (approved by the FDA in 2005 for the treatment of myelodysplastic syndrome) and its sister compound 5-aza-2'-deoxycytidine act on epigenetic regulation. However, the number of clinical trials with these agents in patients with solid tumours is small and responses are low when they are compared directly with conventional therapy.

Figure 1: Levels of therapeutic interventions

- Genetic level
- Transcription
- Translation
- Regulatory level
- Cellular level
- Organ level (tumour - stroma)

Figure 2: Angiogenesis driving mutations

- COX-2
- VEGF
- Mutated SMAD4
- Invasive adenocarcinoma
- Inhibition of dendritic cells
- Tumour stimulation
- Angiogenic switch
Promoter hypermethylation is indicative of poor prognosis, but indicative of benefit from therapy with fluorouracil, particularly for long-term survivors [6]. In parallel, histone deacetylase inhibitors are currently being developed as a complementary strategy to foster expression of repressed tumour suppressor genes. Among them, vorinostat has already been approved by the FDA in the treatment of cutaneous T-cell lymphoma.

The limited success of the strategies mentioned suggests that the focus of our attention has to be shifted from the classic cellular triad "gene - transcription - translation" to regulatory processes acting at the cellular, the tissue, and the organ level including tumour-stroma interactions (Figure 1). Surprisingly, this leads us back to the Vogelstein model, where early genetic mutations such as APC or KRAS drive the expression of COX-2, which in turn induces the angiogenic vascular endothelial growth factor VEGF (Figure 2). Because the angiogenic switch - the stage of steady support of the malignancy by tumour vessels - is a decisive point for almost every type of cancer, antiangiogenic strategies have proven to be so successful in combination with chemotherapy. The neutralisation of VEGF aims not only at the malignant cell itself, but also at fibroblasts of the stroma as a relevant contributing VEGF source. The detailed understanding of lymphangiogenesis, which is driven by VEGF-C and VEGF-D, is likely to open novel strategies against invasion of the lymphatic system. In this context, it is worth noting that one of the angiogenic factors, PD-ECGF is better known as the thymidine phosphorylase, the enzyme which guides the last step in the activation of capecitabine to fluorouracil. Thymidine phosphorylase is, therefore, a candidate for both a prognostic and a predictive factor.

As invasion starts with the proteolytic degradation of the extracellular matrix, matrix metalloproteinase definitely play their role in the progression of the disease. Several years ago, this was convincingly demonstrated for metalloproteinase-9 in colon cancer [7]. A therapeutic strategy to exploit this essential phenomenon is still lacking however.

The latest tumour model, the stem cell concept, applies to solid tumours. In contrast to the classic view, the stem cell concept suggests that only a minority of tumour cells are tumourigenic and that cancer is a disease of the aberrant stem cell. Vice versa, the elimination of the malignancy is dependent on the eradication of the tumour stem cell pool.

All those models point to ways of treating malignant tumours. Some of them have been successfully exploited to another step forward in oncology. We need to integrate the current models in the near future. The cancer stem cell and the epigenetic cancer cell progenitor concepts may have a common basis when investigated in detail. But synthesis of the current models demands much more: it has to embrace the steps down from the cell to the cellular processes (where novel regulatory entities such as micro-RNAs are being found), but at the same time unify the view up at the tissue and organ level paying close attention to the tumour-stroma interactions (Figure 3).

In summary, there is a complex interplay between tumour biology and tumour pharmacology that is not always understood. Our capacity to bridge these gaps will determine the pace of implementation of novel and rational pharmacologic concepts. Models are a decisive and indispensable impetus in this process.

Figure 3: Future approach for integrative therapeutic interventions

<table>
<thead>
<tr>
<th>Regulative level</th>
<th>microRNA Epigenetics</th>
<th>EGFR COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular level</td>
<td>Stem cell</td>
<td>Organ level (tumour-stroma) VEGF, MMP</td>
</tr>
<tr>
<td>TP Thymidine phosphorylase; MMP Matrix metalloproteinase</td>
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References

Pharmacoeconomic trends in Germany: searching for evidence?

We have never had such a hot, controversial or frustrating debate on economic evaluation of drugs in Germany as nowadays. Although there is a long tradition of economic research in health care and economic evaluation of health services in Germany, and widely accepted guidelines for economic evaluation have been published in the past, the discussion seems to be deadlock right now [1].

What is the background of this current battle between the IQWiG and the scientific health economic community? 2007 was the year of a major healthcare reform in Germany: the so-called “Statutory Health Insurance Competition Enhancement Act” (GKV-WSG). Among other significant changes in the sickness fund system (introduction of a uniform contribution to sickness funds, the foundation of a new Federal Association of Statutory Health Insurances, higher barriers to join private health insurers), sections 31, 35b and 130a were incorporated into German law. According to section 35b the IQWiG now has the obligation to conduct cost-benefit analyses for pharmaceuticals. The results of those cost-benefit analyses will be used by the Federal Association of Statutory Health Insurances to set maximum reimbursement prices for drugs (section 31 (2a)). In addition, section 130a(8) allows sickness funds and pharmaceutical companies to negotiate discounts for drugs which are binding for all pharmacies.

Before the IQWiG is ready to start conducting the first cost-benefit analysis for drugs, it has to develop and publish its methodological guide for cost-benefit analyses which by law have to be “based on the international standards of evidence-based medicine and health economics acknowledged within the respective expert circle” under section 35b. At the end of January 2008, a draft version of the methods paper was released to the public. Leading author of this paper is Jaime Caro who works for the US consultancy firm UBC and who was hired by Peter Sawicki, the President of IQWiG, to develop the methods for Germany.

This paper was a big surprise not only to the German scientific community but to everyone working in this field. It contains very little information on how the IQWiG intends to measure and evaluate cost and benefits. That information is hidden in appendices, which have not been released yet. Instead it introduces a new concept – called “efficiency frontier” – for calculating the “appropriate” reimbursement price for innovative compounds on the basis of already existing (and older) drugs in the same therapeutic area. In addition to the description of the new concept, the paper contains many misleading errors, inconsistencies and formal flaws. The IQWiG received more than 50 comments and an extremely critical letter signed by the 29 leading German health economists.

What is the basic idea of the efficiency frontier? Actually the idea can be put very simply: “If intervention A costs twice as much as intervention B (…), A should produce at least twice as much value as B” [3]. In the first step, the cost and benefits of existing drugs used in a certain therapeutic area are taken and plotted in a benefit-cost diagram. Afterwards the cost-benefit ratio of those drugs is extrapolated beyond the drug with the highest benefits and costs. If new drugs are above this cost-benefit extrapolation line, the reimbursement price will be set below the market price. Only if the cost of a new drug is less than the price projected by the extrapolation, will the drug be fully reimbursed.

As the efficiency curve looks (and sounds) like the “efficiency frontier” in Markowitz’s portfolio selection theory of risky assets and the “efficiency frontier” known from production theory, one might think that the IQWiG concept is founded on economic theory. However, this is not true. Neither Markowitz nor economists working on production optimisation have suggested extrapolating the curve beyond existing assets or efficiency points to derive the fair price of new risky assets or production points. The IQWiG approach is simply a mixture of two known concepts, which do not fit together: one taken from portfolio selection theory and another one from economic evaluation theory, called the “incremental cost-effectiveness ratio (ICER)”.
What is the rationale of the IQWiG approach? Firstly, the IQWiG strongly believes that the German healthcare system is in all aspects totally different from other systems, so that internationally accepted standards of economic evaluation cannot be employed in Germany. Secondly, it tries to avoid an overall externally given threshold for a cost-effectiveness ratio, e.g. GBP 30,000/QALY, which defines cost-effective innovation from the payer’s point of view. And thirdly, the IQWiG believes that a formula exists, by which one can determine an *internally generated* specific threshold for innovative new drugs. This would allow the IQWiG to set the reimbursement price, and not leave it to the Federal Association of Statutory Health Insurances. Economists know that this formula is an illusion and that it is a fatal misconception that anyone can set maximum prices without knowing the overall willingness to pay of the payers.

There is no doubt that the current IQWiG approach is inappropriate as a starting point for health economic cost-benefit assessment in Germany. The efficiency frontier concept has neither foundation nor reasoning in economic theory and is untenable when applied to solidarity-based health insurance. Therefore it remains an open question on what the future of cost-benefit analysis will be in Germany. I would recommend that providers of health services focus on providing sound scientific and transparent studies showing the benefit and the cost of their products, instead of paying too much attention to the first misleading attempts of the IQWiG to develop something new and unknown in the field of health economic evaluation technique.

References
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**ESOP News**

**Masterclass in oncology pharmacy practice**

Some course participants kindly gave feedback on the first ESOP masterclass organised by Professor Per Hartvig and Eva Honoré in Ishøj, Denmark 5-7 November 2007.

Attendees came with different experiences and expectations. Visnja Kopecki was excited since her hospital pharmacy was the first in Croatia to prepare cytotoxic drugs for wards and although she had been doing this for a year, she wanted to check her knowledge. Nils Kallberg made the point that “undergraduate pharmaceutical courses have to cover many diverse topics but often not specialisation in hospital pharmacy with subtopics such as paediatric, nutritional or oncology pharmacy”. Praise was unanimous for the “high quality speakers from different European countries” who presented the lectures and the “quiet, relaxing environment” provided by the course leaders. Two attendees appreciated the reasonable price of the course, thanks to the well chosen “homely” hotel; the accommodation was “good, meals were very good”.

Expectations were “high and realised in the field of lectures” by some, while Dr Xavier Armoiry “had personally never seen a variety of closed systems that prevent pharmacist injuries”, so different aspects appealed to different people. Everyone enjoyed discussing the course with colleagues and the informal conversations occasionally filled gaps not covered by the course. The highlight of the week was a banquet in the beautiful small town of Køge.

No course is complete without an examination! Nils commented: “This examination had a friendly and playful attitude but it made a good abstract of what had been taught during the days. For future participants I strongly recommend looking through the printed material and making your own notes before the examination.” Xavier suggested a lecture about economic issues for the next course.

Two final comments: “A great human experience as I met colleagues from 14 different European countries giving us all a concrete example of what EU means” and “Right after I came back I made some changes and improvements”. What more can you say?

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Complementary and alternative medicine in cancer patients — Jens Büntzel, MD, PhD; Ralph Mücke, MD; Frank Bruns, MD; Oliver Micke, MD, PhD

One thousand and thirteen cancer patients were interviewed in five German cancer centres, 30% reported a subjective improvement in quality of life due to the use of complementary and alternative medicine (CAM). The high rate of CAM use and possible interactions with basic anticancer-therapies, e.g. radiotherapy, are reasons to extend CAM anamnesis.

Introduction
CAM is defined by the US National Center for Complementary and Alternative Medicine as any medical and healthcare system, practices and products that are presently not considered to be part of conventional medicine, as practised by holders of MD degrees and allied health professionals [1]. Alternative oncology summarises all methods that are used instead of the conventional anticancer therapy. Complementary medicine represents additional treatment options intended to control symptoms of the disease and treatment, and enhance the quality of life. Over time, some complementary methods are proven safe and effective and become part of mainstream cancer treatment [2]. In order to evaluate the role of CAM in clinical practice, the German Working Group “Trace Elements and Electrolytes in Oncology” conducted a descriptive multicentre study investigating the patterns of CAM use in cancer patients before, during and after radiotherapy.

Methods
A total of 1,013 patients (median age 60 years, 53% male) were included. The study population consisted of consecutive patients seen at five cancer centres in Germany. Only 15 patients (1.5%) refused to participate. We excluded patients with Karnofsky performance status lower than 70%, because they are generally not independent in their usual daily life and medical decision making.

The study was conducted as a semi-structured face-to-face interview based on a standardised questionnaire. Demographic data were registered as well as different types of CAM use. Nine categories of CAM were adopted from the literature [3, 4] and are listed in Table 1. Patients were assessed for the effects of CAM on the quality of life using a subjective semi-quantitative scale. They were also asked for their sources of information regarding CAM.

Results
Patients
The study population mainly consisted of patients suffering from head and neck cancer (n = 334) and breast cancer (n = 294). Smaller subgroups were patients with prostate cancer (n = 81), lung cancer (n = 81), rectal cancer (n = 61), Hodgkin lymphoma (n = 61), Non-Hodgkin lymphoma (n = 51), renal cell carcinoma (n = 40) and other malignancies (n = 10). At the time of interview 238 patients had locally confined, 386 distantly spread disease, some were current smokers (n = 258) and 223 drank alcohol regularly.

Patterns of CAM use
Fifty-nine percent of all patients reported using CAM during the last four weeks. Multiple CAM use was common (mean 3 methods, range 1-8). Significantly more female than male patients (66% vs. 34%) used CAM. CAM users were younger than non-users (56 years, 62 years). Univariate analysis also revealed a positive strong correlation between CAM use and more advanced tumour stages as well as radiotherapy treatment. Smoking and alcohol consumption were less frequent in patients using CAM. CAM use was most frequent in breast cancer patients (91%), followed by patients with Hodgkin’s disease (83%), other gynaecological malignancies (60%), renal cell carcinoma (50%), rectal cancer (50%) and prostate cancer (47%). The frequency of CAM use was lowest in head and neck cancer patients (36%).

Most frequently used CAM therapies were vitamins (18%), mistletoe extracts (15%), selenium (10%), other trace element preparations (7%), thymus preparation (5%) and homeopathy (4%). Prayer (6%) was the most important complementary spiritual measure.

Reasons for CAM therapy
The reasons most frequently reported for using CAM products and therapies were “supporting the conventional treatment” in 46% of patients as well as “feeling better” in 23%. Physicians (62%) and pharmacists (51%) were the main information givers of the interviewed patients. Newspapers, the Internet or other media were used by a minority (<15%).

CAM impact on quality of life
The patients reported an improvement in 304 cases (30%), in 34% (n = 344) there was no subjective change and 5% (n = 51) reported a worsening of their quality of life or side effects due to CAM use. A large number were indecisive (31%). Differentiation according to type of CAM showed that patients using vitamins had a significantly higher rate of subjective improvement than those using homeopathy, thymus and mistletoe preparations or spiritual measures (p<0.05).

Discussion
The majority of cancer patients treated with radiotherapy use at least one method of CAM. The typical CAM user is female, young, suffering from breast cancer, non-smoker, non-drinker, has advanced disease and is being treated with the intention to cure. A large number of other studies also find that breast cancer patients...
The majority of cancer patients use CAM, particularly in the form of vitamins, mistletoe preparations and selenium. In order to identify these patients, to avoid interactions with standard anticancer treatment, waste of money, as well as bias in clinical trials, pharmacists and oncologists should include questions about CAM use when taking the patient’s history. Only with a detailed knowledge of the efficacy, toxicity and cost-effectiveness of CAM will the pharmacist and/or oncologist be able to give patients the information they expect and prevent patients getting their information from doubtful sources. To evaluate the benefit or potential risks of such treatment further studies are clearly warranted.

**Table 1: Categories of CAM**

<table>
<thead>
<tr>
<th>Category of CAM</th>
<th>Examples</th>
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<tbody>
<tr>
<td>(1) Special diets</td>
<td>Vegetarian, vegan, macrobiotic, and Gerson diets</td>
</tr>
<tr>
<td>(2) Psychotherapy</td>
<td>With social worker, psychologist, psychiatrist, or support group</td>
</tr>
<tr>
<td>(3) Movement and physical therapy</td>
<td>Exercise, yoga, tai chi or chi gong, chiropractic or osteopathic manipulation, and massage</td>
</tr>
<tr>
<td>(4) Mind/body therapy</td>
<td>Imagery or visualization, hypnosis, meditation, biofeedback, energy healing or therapeutic touch, journaling, aroma, colour and music therapy</td>
</tr>
<tr>
<td>(5) Spiritual practices</td>
<td>Prayer for self and prayer/spiritual healing by others</td>
</tr>
<tr>
<td>(6) Nutrition, co-factors and supplements</td>
<td>Vitamins, enzymes, trace elements (in particular selenium), herbs, melatonin, shark or bovine cartilage, and Ayurvedic and folk remedies</td>
</tr>
<tr>
<td>(7) Traditional medicine</td>
<td>Chinese and Tibetan medicine, acupuncture, herbal preparations</td>
</tr>
<tr>
<td>(8) Immuno-augmentative treatment</td>
<td>Mistletoe extracts, thymus preparations</td>
</tr>
<tr>
<td>(9) Other approaches</td>
<td>Homeopathy, counselling, bio electromagnetic therapy, alchemy, shamanism, oxygen therapy</td>
</tr>
</tbody>
</table>

are far more likely to be CAM users compared with those with other tumour types [5, 6]. Another group with a very high prevalence to CAM use (83%) are patients with Hodgkin’s disease [3]. This is also described in the literature. These results must be interpreted carefully, because patients suffering from Hodgkin’s diseases are young, with different social structures and a better prognosis than the other subgroups analysed. Consistent with our study, the lowest rates of CAM use have been seen in head and neck cancer patients [7]. Likewise we have also identified smoking and drinking habits as relevant predictors for CAM use.

Vitamins, mistletoe preparations, minerals and trace elements were the most popular preparations in our study. In contrast to the literature [3, 5, 6] we found two distinctive features in the distribution of CAM use:

- The low rate of spiritual practices - we used strict criteria for spiritual measures. A third of our patients came from East Germany with a more atheistic population.
- There was a high frequency of use of mistletoe preparations. This herbal remedy is popular in German-speaking countries, but is seldom used in North America or other parts of Europe.

Although side effects were seldom reported and most CAM therapies can be regarded as harmless, potentially dangerous CAM-drug interactions can occur [8]. The concurrent use of antioxidants can diminish or enhance effects of chemotherapy or irradiation. A responsible physician or pharmacist should ask about self medication and in particular, what type of herbal preparations are being used. They must be aware of possible interactions and in doubtful cases they should warn the patient to stop CAM treatment. On the other hand, pharmacists and physicians have to be able to inform patients about complementary methods, the risks and possibilities. Remarkably, the growing role of the Internet as a source of information on CAM is under-represented in this study.

**Conclusion**

The majority of cancer patients use CAM, particularly in the form of vitamins, mistletoe preparations and selenium. In order to identify these patients, to avoid interactions with standard anticancer therapy, waste of money, as well as bias in clinical trials, pharmacists and oncologists should include questions about CAM use when taking the patient’s history. Only with a detailed knowledge of the efficacy, toxicity and cost-effectiveness of CAM will the pharmacist and/or oncologist be able to give patients the information they expect and prevent patients getting their information from doubtful sources. To evaluate the benefit or potential risks of such treatment further studies are clearly warranted.

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3 Department of Radio-oncology, St Franziskus Hospital Bielefeld, Germany

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   URL: http://nccam.nih.gov/health/whatiscam/
Cisplatin combined with other drugs - how drugs affect one another and the patient

The problem of cisplatin’s kidney toxicity was solved when it was discovered that hydrating the patient markedly diminished toxicity with little or no loss of anticancer activity [1]. We wondered if nephrotoxicity is affected when other drugs are given concomitantly. We followed one such patient.

**History**
Mr KH was 63 years old, weight 105 kg, height 172 cm. According to his hospital file, he suffered from hypertension and type II diabetes mellitus. He came to hospital because of bladder pain.

**Treatment and progress**
At admission a transurethral resection was performed, detecting a solid tumour G3, corresponding to high-grade urethra carcinoma. The subsequent histological research showed infiltration of the tumour into the smooth muscle. The treatment began with gemcitabine/cisplatin. In the meantime, the patient became febrile. Suspecting it was caused by a urine infection, the patient was given the antibiotic combination piperacilin/tacobactam. When the urine culture showed multiresistant *Staphylococcus aureus* the treatment was immediately changed to linezolid. Laboratory tests showed decreasing renal function, so the chemotherapy was changed: carboplatin replaced cisplatin. Carboplatin shows the same mechanism of action as cisplatin, although here haematological toxicity appears as the main side effect. The patient was informed and the next three cycles were given.

**Previous medication**
Esomeprazole tablet 40 mg 1-0-1, metformin tablet 850 mg 0-0-1, lisinopril/HTC tablet 1-0-0, paracetamol tablet 500 mg 1-1-1.

**Laboratory tests**
The patient was monitored regularly. Laboratory tests showed that creatinine values were very high (1.75 mmol/L), while at the same time clearance values were about normal (60 mL/min/1.7 m²). This mismatch is a deficiency of the Cockroft-Gault formula, often used for clearance calculations. The formula considers variables such as age and weight and is adjusted for an average patient. Our Mr KH has a Body Mass Index of 35.5 and hence this formula is not representative for him. The renal function was even more impaired than the values showed.

**Discussion**
We wanted to see how co-medication affected the renal function, so we looked more closely at the pharmacodynamics of the individual drugs. The patient’s fever with elevated C-reactive protein values was a consequence of an infection. The patient was given a combination compound tazobactam/piperacillin IV. Both drugs were largely unchanged in the urine. But these drugs could not have accumulated, because of the rapid switch to linezolid. Linezolid’s total clearance does not change as the renal function falls, therefore, it does not threaten the kidneys [2].

For his high blood pressure Mr KH was given lisinopril/HTC. There are reports of lisinopril further reducing restricted renal function, even at low dose [3]. But according to Brilliant [4], lisinopril causes less microalbuminuria than Ca²⁺ blockers and our patient had protein in the urine (30 mg/dL). The EUCLID study [5] also reports the progression of renal insufficiency even in patients with albuminuria and the protective effects of lisinopril on the kidney - that makes it a very good choice for our patient. But lisinopril alone is often not enough for most patients, including ours. He was taking HTC in addition. Thiazides operate by blocking the transport system in the proximal tubule, the very same place where cisplatin works. There are also reports of prolonged neutropenia with HTC in cisplatin patients, making the drug inappropriate in this case.

For his diabetes treatment, Mr KH got metformin. This can accumulate in renal insufficiency and cause the build-up of lactate, which may result in life-threatening acidosis, but it is not strictly contraindicated in such patients [6]. Nevertheless, laboratory data here showed a constant increase of GGT and LDH (131 U/L, 280 U/L), and that would be ample reason to change the antidiabetic drug. We suggested a sulfonylurea, in this case gliquidone because of the low percentage of renal elimination (just 5%).

The patient was also taking paracetamol, which is metabolised in the liver to glucuronic acid and sulphate conjugates. Due to the patient’s renal impairment, the ability to excrete such polar metabolites is much reduced and when taken repeatedly, accumulation of those metabolites must be expected [7]. There are also reports that paracetamol causes kidney damage through apoptosis of proximal tubule cells, activating enzymes such as caspase 3 and 9, and again this is the same mechanism of action as cisplatin.
Conclusion
Renal impairment here was the result of interaction between several drugs regarded as harmless when given alone. Therefore medical therapy should be carefully individualised, considering each drug and the condition of the patient.

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References

Comment

Placebo: money for nothing?

That placebos can cure everything is well known. They have a long history with witch doctors, faith healers, and even modern physicians. The placebo effect in pain is partially due to release of brain endorphins, which activate the opioid-serotonergic endogenous pain-inhibitory system. Thus the placebo effect is real in the sense that it has its structural and biochemical substrate. Adrenocorticotropic (ACTH) and proopiomelanocortin (POMC) are released in parallel with endorphins. The varied effects of these neuropeptides may explain the placebo effect in a number of different clinical conditions.

Placebo, this most potent of medicines, comes to the aid of everyone, not just those lucky enough to receive placebos in a medical testing programme. Every drug tested would prove effective if special steps had not been taken to neutralise the placebo effect. This is why drug tests give half the patients the new medication and a half a harmless substitute. These tests prove the value of placebos because a large proportion of the patients taking them are cured even though the placebos are made from substances that have been carefully selected to be useless. The actual curing power of placebos probably stems from the faith of the patient in the treatment. This suggests that cure rates in the 40% range could be expected even when patients know their problems are incurable if given placebos under the guise of a proven cure. In a recent meta-analysis Kirsch and co-authors could even show that there was no significant difference between placebos and some common antidepressants (SSRIs) in mild to moderate depression when including data from unpublished trials.

Most people feel that the lucky patients in a drug test get the experimental drug because the real drug gives them a chance to be cured. In the effort to quantify the effect of these drugs, most investigations fail to assess the placebo effect as a therapeutic intervention as they do not incorporate non-treatment controls.

Analysis shows that possibly patients getting the placebo are the lucky ones because they are going to be cured without risking any adverse effects the new drug may have. The drug may well be found to be worthless and to have severe side effects.

Unfortunately, placebo treatment cannot operate as a non-profit business. The non-profit idea is ruled out because the first rule of medicine is never to give free medicines. Public health services know that medicine not paid for by patients is often not taken or not effective because the recipient feels the medicine is worth just what it costs him. Even though the patients would not know they were taking sugar pills, placebos cost so little that the patients would have no faith in such a cheap treatment.

Even though it is against their principles, health professionals using placebos must, therefore, charge fees for placebo treatment. Even higher prices for placebos than for standard treatment might be considered.

Sabine Thor-Wiedemann, MD
Professor Günther J Wiedemann, MD, PhD

References

Editor’s note: Opinions expressed in this article are views of the authors.
**The new era of trabectedin in soft tissue sarcomas**

Prognosis for patients with soft tissue sarcomas remains poor and pharmaceutical research in this area is limited. Therefore the regulatory approval of trabectedin for the treatment of adult soft tissue sarcomas is an important milestone.

**Introduction**

Results of first-line chemotherapy in adult advanced soft tissue sarcomas remain disappointing. Only two drugs, doxorubicin and ifosfamide, have demonstrated a relatively consistent single-agent activity, yielding response rates of 10-25%. Multidrug regimens have not demonstrated any advantage in terms of overall survival, when compared to single agent doxorubicin given at optimal doses. In the past 20 years, new drugs have not demonstrated any relevant activity in advanced soft tissue sarcomas and prognosis for patients remains dismal. So patients who fail or relapse after anthracycline-based regimens are appropriate candidates for new investigational strategies. But despite this high unmet medical need, pharmaceutical research in soft tissue sarcomas (STS) is limited.

Trabectedin (Ecteinascidin, Yondelis, ET-743, PharmaMar, Spain) in September 2007 obtained marketing authorisation as therapy for adults with advanced pre-treated STS. This is the first regulatory approval in this category in the past 25 years.

**Mechanism of action**

We have nature to thank for many anticancer compounds. Trabectedin is a tetrahydroisoquinoline compound isolated from the sea squirt Ecteinascidia turbinata and consequently produced by semi-synthesis (see Figure 1). Trabectedin is a unique agent that interacts with DNA by binding covalently to the DNA minor groove. It blocks cell cycle progression in the G2/M phase through a p-53-independent apoptotic process and inhibits the transcriptional activation of inducible genes [1]. Trabectedin has shown important preclinical activity against a number of human solid tumour cell lines and xenografts, including sarcomas, with minimal or no cross-resistance to several conventional chemotherapeutic agents.

**Early trials**

Based on these preclinical findings, 163 patients were included in five phase I studies assessing six different schedules of administration with doses of trabectedin ranging from 0.05 mg/m² to 1.9 mg/m² with transient transaminases elevation and neutropenia the dose-limiting toxicities. Activity (one complete remission and three partial responses) was seen in patients with advanced STS using the 24-hour and 3-hour infusion schedules. Due to the large amount of information available with the 24-hour continuous infusion, this schedule was selected for the phase II trials in STS at the recommended dose of 1.5 mg/m².

The results of the three phase II trials are listed and summarised in Table 1, with the median progression-free survival (PFS) according to response categories.

The clinical activity/efficacy of single-agent trabectedin has been demonstrated in heavily pre-treated patients with advanced STS, with a median duration of response of approximately 9-12 months and with a 6-month PFS rate of 24-29% [2]. Although the objective response rate in patients with anthracycline-resistant advanced STS did not exceed 10% overall in several phase II clinical trials, this drug does result in clinically meaningful control of disease. PFS exceeded 25% at six months, compared with the historical best of 14% in patients treated with the well known agents ifosfamide and dacarbazine [3].

The median overall survival for patients receiving trabectedin as second/third line chemotherapy was unusually high in this cohort of heavily pre-treated patients, more than nine months. This could be explained by several factors:

- a similar favourable outcome of patients whatever the number of prior chemotherapy lines, even in patients who had previously had two chemotherapy regimens
- a high proportion (30%) of patients receiving six or more cycles, with some patients receiving more than 15 courses, which is
uncommon in screening studies testing new cytotoxic drugs
- the combination of a lack of cumulative toxicities and a high median time to objectively observed regression (5.3 months), which emphasised the need to continue treatment even in patients with stable disease
- the high rate of patients who clearly benefited from the drug not only in terms of the WHO/Response Evaluation Criteria in Solid Tumours (RECIST) response criteria but in terms of tumour control including minor tumour regression, prolonged stable disease (around one third of patients) and loco-regional treatments (complete resection of metastases in responding patients).

Trabectedin is the first cytotoxic agent to achieve prolonged stabilisation in previously progressing patients in the field of palliative care for advanced STS.

Trabectedin was also evaluated in 35 chemotherapy-naive patients with advanced STS with the same schedule and demonstrated an overall clinical benefit rate of 20% and median duration of response of 16.5 months [4].

Toxicity of trabectedin

The toxicity profile observed in pre-treated patients included in these phase II trials corroborates the results observed in previous phase I studies testing the 24-hour infusion of trabectedin at the recommended dose. Reversible, transient, asymptomatic, grade 3-4 elevation of transaminases (between the third and seventh day after dosing) was seen in about 50% of patients, representing 20% of all cycles. This non-cumulative toxicity was reduced by the prophylactic use of dexamethasone as an antiemetic agent and did not preclude prophylactic use of dexamethasone as an antiemetic agent and did not preclude the high rate of patients who clearly benefited from the drug not only in terms of the WHO/Response Evaluation Criteria in Solid Tumours (RECIST) response criteria but in terms of tumour control including minor tumour regression, prolonged stable disease (around one third of patients) and loco-regional treatments (complete resection of metastases in responding patients).

patients. This is in contrast to the cardiac and renal toxicities of doxorubicin and ifosfamide respectively which preclude any long-lasting treatment with these two drugs, even in responding patients.

Some uncommon serious adverse events with multi-organ failure occurred in a few patients included early in these trials. A stringent and careful analysis of all severe toxicities (grade 3-4) observed in these patients established a high correlation with an abnormal alkaline phosphatase (ALP) baseline value and a rise in ALP and/or bilirubin in between cycles. After a protocol amendment (October 1999), the incidence of all serious toxicities was significantly reduced in patients subsequently included in all trials worldwide.

Phase II randomised trial and registration

A higher proportion of objective responses and prolonged stabilisations was documented in these phase II (European and US) studies for patients with primary liposarcomas and leiomyosarcomas, compared with those of other STS subtypes.

Based on these observations, a randomised phase II study was conducted in patients with these two histological subtypes of sarcoma after failure of prior anthracyclines and ifosfamide (second/third line chemotherapy). This pivotal trial compared two different schedules of trabectedin: a weekly schedule (0.58 mg/m² per week, 3 weeks/4, in 3-hour infusion) and a 3-weekly schedule (1.5 mg/m² in a 24-hour continuous infusion) with the time to progression (TTP) as main endpoint. After the inclusion of 270 patients, an independent data monitoring committee recommended stopping the randomisation and switching all patients on the weekly schedule to the 3-weekly therapeutic arm.

The results of this prospective study were reported at American Society of Clinical Oncology (ASCO) congress in May 2007 and were recently presented at the European Cancer Organisation (ECCO) congress in September 2007 [5]. Baseline characteristics were comparable in both therapeutic arms, especially the median number of metastatic sites (2) (range: 1-7) and the median number of prior regimens (2). The median number of cycles given was 2 (range: 1-21 cycles) in qwk-3 h (weekly schedule) versus 5 (1-37) in the q3wk-24 h (3-week schedule). Nineteen percent of patients received more than six courses in the qwk-3 h versus 39% in the q3wk-24 h. A reduction of tumour burden was reported in 50.2% of patients receiving the continuous schedule versus 32.4% in the weekly schedule (p = 0.0008) (Figure 2).

In protocol-specified primary analysis, the median (95% CI) time to progression (TTP) was 3.7 (range: 2.1-5.4) vs. 2.3 (range: 2.0-3.5) months [HR: 0.734; p = 0.0302] favouring the q3wk-24 h arm. The study met its primary endpoint, showing a statistically significant 27% reduction in the risk of progression in favour of the q3wk-24 h schedule (Figure 3). The median progression-free survival (PFS) was 3.3 (2.1-4.6) vs. 2.3 (2.0-3.4) months.

<table>
<thead>
<tr>
<th>Response</th>
<th>N = 189 (%</th>
<th>Tumour reduction</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (0.5%)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>13 (7%)</td>
<td>67%</td>
<td>7 months</td>
</tr>
<tr>
<td>MR</td>
<td>11 (6%)</td>
<td>35%</td>
<td>7 months</td>
</tr>
<tr>
<td>SD</td>
<td>75 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD &gt;6 months</td>
<td>32 (17%)</td>
<td></td>
<td>8 months</td>
</tr>
</tbody>
</table>

Table 1: Efficacy of trabectedin (1.5 mg/m² in 24-hour continuous infusion) in advanced soft tissue sarcoma: pooled analysis of the three phase II trials
Best results: trabectedin administered in 24 hours continuous infusion allows a significant decrease of tumour burden (p = 0.0008).

There is a statistically significant 27% reduction in the risk of progression in favour of the q3wk-24 h schedule.

**Trabectedin in combination**

The cytotoxicity of trabectedin and doxorubicin shows a synergistic antitumour effect mediated via apoptosis in tumour cell lines and this combination in preclinical studies in human sarcoma-bearing mice suggested a synergistic effect. A recent phase I trial with 41 chemotherapy-naive patients with advanced STS defined the maximum tolerated doses as trabectedin 1.1 mg/m² and doxorubicin 60 mg/m². Although the primary goal of the study was not to measure treatment response, five (12%) patients achieved a partial response, and 34 (83%)
maintained stable disease and the median progression-free survival was 9.2 months. This combination deserves further development in this setting.

In addition the combination of liposomal doxorubicin and trabectedin is under evaluation in advanced/relapsed ovarian cancer and a phase III registration study comparing this combination versus trabectedin alone has been completed.

New developments with trabectedin
The emergence of new molecular targets and genetic profiles in various histological subtypes of sarcomas, such as imatinib in gastrointestinal stromal tumour, has clearly opened a new era in the management of STS. There is now major interest in dissecting the potential role of trabectedin in specific sarcoma sub-types. New recent data demonstrates a dramatic impact in patients with advanced pre-treated myxoid liposarcoma. This category of liposarcoma relates to a reciprocal 12:16 translocation that leads to a chimeric DNA-binding protein, FUS-CHOP, which acts as a transcription factor. Early data indicates the capability of Yondelis to down-regulate the activity of genes that are FUS dependent.

Fifty-one patients with myxoid liposarcoma treated with trabectedin at five referral institutions in an expanded-access programme were retrospectively analysed. Trabectedin was given every 21 days, at a dose ranging from 1.1 to 1.5 mg/m². The results were impressive with a 90% rate of long-lasting objective remissions (51% of objective responses by RECIST criteria) and tumour control (stabilisation with decrease in tumour density or consistent alterations on CT scan), a median PFS of 14 months, and a 6-month PFS of 88% (6). This analysis resulted in the initiation of two prospective studies to assess the value of trabectedin in the treatment of myxoid liposarcoma in the preoperative and metastatic settings. Furthermore, the selective mechanism of action of trabectedin in this translocation-related sarcoma is being studied.

A new project is seeking to characterise the clinical potential of trabectedin in other translocation-related sarcomas which represent around 30% of all soft tissue sarcomas. Additionally, the pharmacogenomic trabectedin-related programme has confirmed a molecular signature, based on a non-functional homologous recombinant DNA repair and an effective nucleotide excision repair that clusters both sensitivity and resistance to Yondelis. The combined expression of low BRCA1 and high ERCC1 identifies a STS patient subpopulation highly sensitive to trabectedin.

Note: An abridged version of this article can be found on www.ejhp.eu

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References

Meeting Report: Pan-Hellenic hospital pharmacists seminar in Cairo

The Chief Pharmacist of St Savvas Oncology Hospital, Athens, writes: “I was deeply moved to visit the heart of Egypt in March 2008, following the footsteps of Hellenism centuries ago. We were amazed to find the respect paid to Alexander the Great by Egypt. Pharmacy, like medicine, is a science based on the knowledge handed down to us from ancient civilisations. The pharmaceutical plants and their curative attributes were long ago written down in books and on papyrus”.

The title of the seminar was “New therapeutic approaches in hospital pharmacy”. The main speakers were Olga Ikonomou, the President of PEFNI (Pan-Hellenic Scientific Association of Greek Hospital Pharmacist), Professor Papaioannou, head of the Faculty of Pharmacy, University of Athens and Professor Tountas of the Faculty of Medicine, University of Athens. Several pharmacists and oncologists also presented topics.

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Tumour lysis syndrome – prevention and treatment

Tumour lysis syndrome is a potentially life-threatening cancer treatment-related complication. It occurs after rapid destruction of malignant cells, which releases cellular breakdown products such as nucleic acids, anions, cations and peptides. The incidence can range from 3 to 20%.

Introduction

Tumour lysis syndrome (TLS), a cancer treatment-related complication, is an acute metabolic disturbance caused by the treatment of malignancy and rapid tumour cell breakdown. The incidence of TLS depends on risk factors and the type of malignancy and ranges from 3 to 20%. The breakdown products from destruction of tumour cells are nucleic acids, anions, cations, peptides including uric acids, potassium and phosphate. The risk of TLS is highest when a patient has the first course of treatment. Renal failure with a reported incidence of 25-38% and death with incidence of 5-14% are the most serious complications.

The laboratory signs of metabolic abnormalities in acute TLS are hyperuricaemia, hyperphosphataemia, hyperkalaemia, hypocalcaemia, metabolic acidosis and renal failure. Typical signs and symptoms depend on the clinical abnormality and can be: arrhythmias, seizures, bradycardia, electrocardiogram changes such as peaked T waves, gastrointestinal symptoms, acute renal failure, anuria, azotemia, lethargy, muscle cramps, tetany, decreased clearance of medications and fluid overload.

Predisposing factors

The risk and predisposing factors are well known: baseline hyperuricaemia, bulky tumour burden (>10 cm), concentrated acidic urine, male gender, sensitivity of the tumour to a particular treatment modality, renal impairment, volume depletion, haematological malignancies with high proliferative fraction, elevated pre-treatment serum lactate dehydrogenase and/or uric acid serum levels and first course of chemotherapy. Uric acid from purine metabolism can precipitate in the renal tubules and cause renal failure with oliguria. The reasons are a high concentration of uric acid and acidic urine. Therefore maintaining the urine flow and alkalisation of the urine are sufficient to reduce precipitation and preserve renal function.

Hyperkalaemia and secondary arrhythmias are the primary causes of death in patients with TLS.

Prevention

Prevention and early management are important if we are to decrease cardiac arrhythmias, seizures and organ failure which are the main reasons for morbidity and mortality. A sufficient risk assessment with prophylactic measures seems necessary. Thiazide diuretics, potassium-sparing diuretics and nephrotoxic medications should not be administered. The cancer care team should not hesitate to consult speciality services such as nephrology or critical care if a need emerges for transfer to the intensive-care unit or for dialysis. IV hydration with 0.9% sodium chloride or crystalloid fluids is very important to achieve a urine output of 100 mL per hour two days before, and continuing for possibly three days after, chemotherapy or until normalisation of electrolyte abnormalities. Patients with pre-existing renal failure benefit from using mannitol or loop diuretics to maintain urine output. To improve the renal excretion of uric acid, make the urine alkaline (pH at or above 7.0) with 50 to 150 mEq of sodium bicarbonate per litre of IV fluid or sodium bicarbonate orally. Patients with hyperphosphataemia or hypercalcaemia should not be alkalised because they are at high risk of the kidneys being harmed by calcium phosphate crystals.

Allopurinol is the drug of choice for prophylaxis of TLS. It acts by inhibiting the enzyme xanthine oxidase; it can be given for about 5-7 days to normalise serum uric acids level. The IV route is only for patients who are unable to take allopurinol orally. Hypersensitivity reactions and renal dysfunction are adverse effects. Amoxicillin, ampicillin, angiotensin converting enzyme inhibitors and thiazide diuretics have been associated with hypersensitivity reactions when combined with allopurinol. The incidence of rash may be increased by penicillins. Allopurinol decreases the elimination of 6-mercaptop-
urine and azathioprine and interacts with capecitabine. The initial dosages are 100 mg in elderly patients and up to 200-300 mg/m² or more for adults depending on renal impairment. Doses >300 mg should be given in divided doses. The dose for secondary hyperuricaemia with chemotherapy is 600-800 mg/day for children <10 years and adults, given in 2-3 divided doses to prevent acute uric acid nephropathy; give for 2-3 days starting 1-2 days before chemotherapy.

Management

Hyperuricaemia

Allopurinol can be used as described above. Rasburicase is unique as a treatment of renal failure associated with TLS in that it catalyses the metabolism of existing uric acid. Other options prevent uric acid formation. Patients who are given rasburicase do not need alkalisation because the drug acts rapidly. Serum uric acid levels fall within four hours.

Rasburicase is a recombinant urate oxidase enzyme which converts uric acid to allantoin, an inactive and far more soluble metabolite of uric acid. Because it is expensive, rasburicase is used for higher-risk patients with worser renal dysfunction or severe hyperuricaemia before therapy. The drug should not be given to patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of haemolysis and methaemoglobinemia. Hypersensitivity reactions are the reason for close monitoring during infusion; no clinical drug-drug interactions have been reported.

Hyperkalaemia

Increasing levels of potassium after cellular breakdown can be dangerous and lead to cardiac arrhythmias or sudden death, especially when hypocalcaemia is also present. Potassium intake should be avoided. Patient with mild hyperkalaemia need sodium polystyrene sulfonate orally or as an enema; it binds potassium in the gastrointestinal tract. Insulin, dextrose or inhaled ß-agonists will quickly shift potassium out of the extracellular compartment; sodium bicarbonate has the same effect if acidemia occurs. If the electrocardiogram changes, IV calcium should be given to prevent arrhythmias by stabilising the cardiac membrane. Dialysis is necessary if cardiac effects increase. The purpose of haemodialysis or haemofiltration is to remove uric acid, phosphate and potassium and to control fluid volume.

Figure 1: Recommended strategies for prevention and management of TLS

Low risk
Continue standard practice, monitor for three days after chemotherapy

High risk: PREVENTION STRATEGIES
1. Minimise risk of TLS
   a) Eliminate exogenous sources of potassium and phosphate such as dietary supplements
   b) Discontinue or avoid drugs that may increase potassium (potassium-sparing diuretics, ACE inhibitors) increase uric acid (thiazide diuretics, proxbenecid) or be nephrotoxic (NSAIDs, IV contrast media, aminoglycoside antibiotics)
2. Maximise prevention
   a) Keep patient in hospital and repeat laboratory tests daily
   b) Administer IV fluids at 2-3 L/m² day
   c) Alkalinate unless patient has hyperphosphataemia
   d) Administer allopurinol

No sign of TLS
Continue hydration and prophylaxis for at least three days post-chemotherapy

 MANAGEMENT
Administer rasburicase. Seek intensive care or nephrology specialist advice, transfer to ICU or use dialysis if necessary

Newly presenting patient
Determine risk of TLS:
   a) risk factors
   b) establish baseline blood parameters

≥1 risk factor + elevated uric acid and/or creatinine at baseline
Acute TLS develops

No risk factors and normal laboratory results

Figure 1: Recommended strategies for prevention and management of TLS
Hyperphosphataemia and hypocalcaemia
The level of inorganic serum phosphate may be high after cellular breakdown, as phosphate excretion is limited by glomerular filtration rate. Any azotaemia will hinder phosphate excretion. The treatment consists of phosphate binders such as aluminium (careful of aluminium-containing products and renal dysfunction), magnesium and calcium salts orally, as well as binding resin sevelamer (Renagel); the effect is to prevent dietary absorption of phosphate with meals.

Symptomatic hypocalcaemic patients with neuromuscular irritation, tetany and cardiac arrhythmias may receive 10 mL calcium gluconate 10% IV to increase serum calcium levels.

Conclusion
A multidisciplinary team is a requisite for preventing most occurrences of TLS. The physician monitors patients for complications, nurses measure urine output and hydration. Pharmacists take a closer look to adjust medication for renal dysfunction. Preventing TLS is important for patients with high grade malignancies with rapid cell breakdown. Identifying patients at risk of developing TLS allows preventive measures to be taken and significantly reduces morbidity and mortality.

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References

Improving the care of anorexia-cachexia patients

Anorexia-cachexia, a complex syndrome, is only variably understood. A pharmacist-led UK team won an award in 2007 and developed a resource pack to enable the systematic assessment and management of the common problems of anorexia-cachexia syndrome (ACS). It contains simple measures to improve patients’ symptoms and well-being.

Introduction
Cachexia, together with anorexia, has been described as “one of the most frequent and devastating problems affecting patients with advanced cancer” [1].

ACS is typified by weight loss, lipolysis, loss of muscle and visceral protein, anorexia, chronic nausea and weakness [2].

It is present in the vast majority of patients with advanced cancer, and can be seen at diagnosis of most upper gastrointestinal and lung cancers [2]. It is known to be an independent indicator of poor prognosis and is associated with a heavy symptom burden for patients [3, 4].

As a syndrome it is under-recognised. The symptoms associated with it are under-reported by patients and often not addressed by medical and nursing staff [5]. Experience suggests that ACS is variably assessed, if at all, by healthcare professionals and management of the problems raised is similarly inconsistent [6].

The exact cause of ACS is not clearly understood. However not surprisingly it is linked to a reduced energy intake and an increased energy expenditure. A number of hormone, neuro-peptide and biochemical signals are disrupted in this syndrome [7]. There is now considerable effort to understand the complex pathophysiology underlying ACS and a number of research projects are focusing on treatments to slow, or reverse the progression of ACS. However a 3-year research project in Durham, UK had the specific aim of improving the experience of ACS for patients. The project began by assessing what currently happened to patients. So baseline reviews were conducted with both staff and patients. Staff attitudes to recognising, assessing and managing the symptoms associated with ACS were reviewed as well as patients’ symptom burden and current treatments. These
reviews then informed a quantitative research project in which prescribing guidelines and shared care agreements were written for several of the medicines. This research showed that standardised assessment and management of ACS can improve the experience for patients [8]. A qualitative piece of work also supported this finding.

This article will focus on the basics of assessment and pharmacological management of the common symptoms associated with ACS. However, relief of the symptoms commonly associated with ACS is not achieved with medication alone. There are useful and important non-pharmacological interventions not mentioned here such as; nutritional supplementation, advice around food and eating and moderate exercise programmes. Much work has been done to show the tensions and anxieties that the symptoms associated with ACS can cause within families [9]. There are strategies that can be employed to help to relieve these tensions amongst patients and their carers. And so the pharmacological management of these patients should always form part of a multidisciplinary approach.

### Assessment

A careful assessment of patients is needed to tailor specific treatments both pharmacological and non-pharmacological. The Patient Generated-Subjective Global Assessment tool is ideally placed to do this. The tool has been validated in cancer patients [10]. It assesses four main areas: weight, food intake, symptoms and function - allowing an excellent overview of

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**Table 1: Suggested treatment for symptoms associated with ACS**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medication</th>
<th>Dose</th>
<th>Prescribing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling full quickly (early satiety)</td>
<td>Metoclopramide</td>
<td>10 mg tds</td>
<td>Before food.                              Titrate to effect, maximum dose 120 mg/24 hours. Review regularly, not for long term use.</td>
</tr>
<tr>
<td>No appetite</td>
<td>Dexamethasone</td>
<td>4 mg mane</td>
<td>After food. Review weekly, maximum course 4 weeks. Reduce gradually to stop.</td>
</tr>
<tr>
<td></td>
<td>Megesterol acetate (+/- Ibuprofen)</td>
<td>160 mg tds</td>
<td>After food. Review after 2 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg tds</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Pilocarpine</td>
<td>5 mg tds</td>
<td>Review after 2 weeks.</td>
</tr>
<tr>
<td></td>
<td>Sugar-free chewing gum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Artificial Saliva (mucin-based)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered taste</td>
<td>Zinc</td>
<td>As zinc sulphate monohydrate 125 mg tds</td>
<td>Check renal function prior to commencement. Review after 2 weeks.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Metoclopramide</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Problems swallowing (review cause)</td>
<td>Oral Candida: Fluconazole</td>
<td>50 mg mane</td>
<td>Review after 1 week, if still present continue for another week. Take oral swab for culture and sensitivities after 2 weeks.</td>
</tr>
<tr>
<td></td>
<td>Mechanical: Metoclopramide</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Sore mouth (review cause)</td>
<td>Oral Candida: Fluconazole</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Ulcers: Topical corticosteroid</td>
<td>Apply to area qds</td>
<td>Review after 5 days.</td>
</tr>
<tr>
<td></td>
<td>Unknown cause: Benzydamine mouthwash</td>
<td>15 mL, 1-3 hourly</td>
<td>Dilute with warm water if it stings.</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Eicosapentaenoic acid</td>
<td>&gt;2 g/day</td>
<td>Titrate dose as tolerated.</td>
</tr>
<tr>
<td></td>
<td>Megestrol acetate</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td>50 mg bd</td>
<td>Unlicensed medicine, register to prescribe. Titrate to effect.</td>
</tr>
</tbody>
</table>

* in descending order of frequency, reported by patients in Durham project
patients status. The scored tool then points to the need for intervention.

As this syndrome is multi-symptomatic very often patients will have polypharmacy. Therefore a drug history is essential to establish which medications are already being prescribed for the symptoms and which could be causing/contributing to the symptoms. A medicines use review is also vital to establish concordance.

In addition, a diet history from patients can be useful information to help decide whether basic dietetic strategies could be employed or if there is a need for specialist dietetic referral/involvement.

Symptoms and treatment
The common symptoms associated with ACS are seen in Table 1 [11]. These frequently reported symptoms can usually be managed by standard medication regimens, also seen in Table 1. The medications used should be prescribed in line with local formulary recommendations and national prescribing information. The guidance should then be tailored to the individual patient, taking into account contraindications and interactions with current drug regimen. A management plan should then be established and communicated effectively with the patient to ensure concordance. As suggested in Table 1 all medications initiated should be reviewed regularly.

Conclusion
It can be seen, therefore, that the standardised, basic assessment and management of the common symptoms of ACS is a straightforward process that can rapidly improve symptom burden for patients. Oncology pharmacists are ideally placed to help manage this condition.

Sponsor
The Durham work has been funded by the charity Macmillan Cancer Support, the main outcome of the project being a resource pack for professionals. This is available to download as the Macmillan Durham Cachexia Pack at learnzone.macmillan.org.uk

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References
Allergic reactions to oxaliplatin therapy – an overview

Overcoming barriers to treatment is very rewarding. A team from Germany suggests a mechanism of action for allergic reactions to oxaliplatin and some practical ways of overcoming them.

**Case reports**
After having received 14 infusions of a modified FOLFOX regimen, a 73-year-old male patient with colorectal cancer suddenly experienced skin problems characterised by extended pruritic erythema on his hands, face and chest during an oxaliplatin infusion. An immediate intravenous dose of 8 mg dexamethasone and 2 mg clemastine relieved his symptoms promptly. Oxaliplatin was re-administered (15th infusion) after a two-week interval and the same type of skin reaction was observed. Nevertheless, during subsequent infusions of the platinum compound the patient did not experience any problems.

Another patient in the Medical Ambulatory Department (70 years, male, colorectal cancer) became symptomatic with a reddish pruritic rash on his hands triggered by oxaliplatin administration. However, since the patient had been given 8 mg of dexamethasone prior to each infusion because he had suffered from therapy-induced fever since the beginning of his chemotherapy, the true extent and real onset of this reaction could not be established.

**Results of literature research**
An allergic reaction to oxaliplatin is probable in more than one out of ten patients [1, 2]. The rising use of oxaliplatin for colorectal cancer could explain the surge in patients showing allergic reactions [3, 4]. Documented reactions vary from mild erythema to life-threatening anaphylactic shock [5] indicating that grades 1-4 allergic reactions may occur, although grades 3-4 occur in only 1-2% of patients [3, 4].

**Allergic reaction** characterised by smooth muscle contraction, capillary dilatation and release of antibodies must be distinguished from *idiosyncratic hypersensitivity*, which is triggered by malfunctioning or non-functioning of defective enzymes, or by a lack of intact enzymes. Santini [6] and Thomas [7] report both idiosyncratic and allergic (IgE-mediated) hypersensitivity reactions to oxaliplatin. In some patients Santini ruled out allergy because of the absence of antibodies (despite symptoms of allergy) and assumed that oxaliplatin is acting as a superantigen based on laboratory findings (IL-6, TNF).

Furthermore, Siu [4] observed that patients were significantly more likely to experience an allergic reaction when they received it as second-line therapy than when having it first line (19.6% vs. 10.2%). In other words patients who had been exposed to other agents first seemed to develop hypersensitivity reactions almost twice as often as untreated patients.

Scientific publications on this subject confirm that allergic reactions are typically observed during platinum infusions 7 to 11 occurring during or very shortly (2-3 hours) after the infusion [4, 7, 8]. In contrast, de Vries [9] reported a female patient who, though receiving oxaliplatin for the first time, experienced dyspnea 20 hours later. Although this patient could be managed with appropriate medication, she suffered from recurrent dyspnea despite appropriate premedication during subsequent infusions and had to stop therapy. Edmondson [10] published a similar case, but was not able to identify oxaliplatin antibodies in his patient.

Whether these spontaneous reactions, occurring early in the course of therapy, are due to antibody-mediated allergy or to idiosyncrasy as described above, needs further studies.

**Documented allergic reactions to oxaliplatin**
- grades 1 to 4
- observed between infusion 7 and 11 of platinum compounds
- occur during or shortly after the infusion (2-3 hours)

**Alternatives to current treatment protocols**
Considering the risk of serious grade 3 or 4 allergic reactions, efforts should be made to establish alternatives to the current regimen [4, 5, 7]. Given the usefulness of oxaliplatin in treatment, prompt cycle discontinuation and switch to another cytotoxic drug should not be automatic; the risks should be weighed against the benefits for the patient.
While no standard measures have been established yet, three approaches have proven beneficial in preventing allergic and idiosyncratic reactions to oxaliplatin [3]:

- Decrease infusion rates, i.e. prolong the infusion times.
- Administer high dose corticosteroids and antihistamines in advance.
- Try desensitisation.

Mostly case descriptions and observations of desensitisation in small patient groups have been published to date [11]. Oxaliplatin desensitisation is based on desensitising protocols established for older cytotoxic platinum compounds [5]. This is not to be understood in the sense of a classical desensitisation procedure where immunogenity may take several months to develop. Non-sensitivity, as described here, may develop within hours although the mechanisms responsible for the rapid immunity have not yet been established.

The desensitisation procedure is based on a pronounced dilution (1:10,000) of the dose, which is subsequently titrated up to the target dose during the infusion period [10, 12]. Edmondson prepared three oxaliplatin dilutions and administered them with each oxaliplatin infusion as shown in Table 1. Therapy was well tolerated without premedication in the patient concerned, who was able to continue treatment successfully.

According to Gammon, desensitisation is justified in patients with grade 3 reactions [12]. Milder presentations may be managed by decreased infusion rate and/or anti-allergic premedication. These results differ from those published by Siu [4], who reported recurrence and, in two cases, aggravation of allergic reactions despite premedication.

**Mechanism of action**

Why do IgE-mediated immediate reactions occur within a fairly well defined time interval and narrow time window? Oxaliplatin has been reported to accumulate in erythrocytes [13]. We suggest that in both of our reported cases irreversible incorporation and thus retention of the substance for the duration of the natural life span of red blood cells was involved. Can cell death of a generation of erythrocytes that have accumulated a maximum amount of platinum lead to the release of a platinum compound which is responsible for these reactions? The answer to this question may contribute to safer treatment in the future.

**Conclusion**

Present published literature agrees that an allergic reaction to oxaliplatin does not necessarily require discontinuation of therapy and that the patient may benefit from careful assessment of treatment options [14]. The small number of reported cases precludes definitive statements about how to prevent these reactions but slow infusion and up-titration to the target therapeutic dose may be considered.

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**References**

2. Eloxantin SPC, Sanofi-Aventis, September 2004.

---

**Table 1: Desensitisation protocol for oxaliplatin allergy**

<table>
<thead>
<tr>
<th>Oxaliplatin concentration (mg/mL)</th>
<th>Dose no.</th>
<th>Volume infused (mL)</th>
<th>Duration of infusion (min)</th>
<th>Dose administered (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>1</td>
<td>0.36</td>
<td>5</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.7</td>
<td>5</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3.5</td>
<td>5</td>
<td>0.175</td>
</tr>
<tr>
<td>0.5</td>
<td>4</td>
<td>0.6</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.2</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>5.0</td>
<td>7</td>
<td>0.6</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1.2</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2.4</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4.8</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>9.6</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>16.6</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>205</td>
<td>175*</td>
<td></td>
</tr>
</tbody>
</table>

Oxaliplatin dose, 85 mg/m² (15-20 minute intervals between doses) [10]

*depending on patient’s body surface area
Most anticancer drugs, it is now well recognised, are potentially hazardous substances, since they are carcinogenic, mutagenic and/or toxic to reproduction (CMR). For this reason, healthcare workers who are involved in the preparation and handling of anticancer drugs can, if they are not adequately protected, absorb potentially harmful quantities of such compounds [1, 2].

Therefore it is important that all people involved with cytotoxic drugs, medical, nursing and pharmacy staff as well as cleaners, transporters, etc. must receive appropriate training relating to their level of involvement. More specifically, they must be aware of the hazards associated with the accidental spillage of cytotoxic drugs. Consequently, procedures and protocols should be drawn up by a multidisciplinary team in each institution and should correspond to appropriate risk management guidelines.

ESOP thanks all partners who help improve safety.

For these reasons, ESOP has decided to suggest standardised labelling to identify highly potent drugs. At the assembly on 24 January 2008 in Hamburg, Germany, ESOP delegates reached a consensus to adopt:

- A written warning “Highly potent medicine, handle with care”
- Yellow as a colour code (yellow is the international colour to warn of danger)
- A unique sign
- A text describing what to do in case of an accident.

The detailed recommendations, the fruits of three years of discussions, are presented in the side box.

The next step will be to publicise this recommendation to all those involved in handling cytotoxic drugs (medical, nursing and pharmacy staff; cleaners, transporters, pharmaceutical companies, wholesalers and health authorities) in order to harmonise labelling practice.

It would also be of great help if the commercial packaging could alert that the drug has CMR effects. Pharmaceutical firms, pharmacists and European governments should collaborate in this safety issue.

References
Cytotoxic drugs are essential in the treatment of cancer, but they are also potentially hazardous substances, that must be kept safely 24 hours-a-day for the protection of those who work with them. The carcinogenic, mutagenic and teratogenic potential of such drugs represent a serious risk to the health of the people involved in the production, preparation and use of these substances.

Working with or near hazardous drugs in healthcare settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukaemia or other cancers [1].

For this reason, guidelines and standards covering the safe handling and preparation of cytotoxic drugs have been published. In 2007 the International Society of Oncology Pharmacy Practitioners (ISOPP) published the standards of practice for the safe handling of cytotoxics; section 2 covers the transport of cytotoxics [2]. All cytotoxic drugs should be packaged, stored and transported in such a way as to prevent damage and subsequent contamination of the environment, the drug itself, and all personnel involved in the routine handling and transportation of these drugs. Suppliers of cytotoxic drugs are requested to design primary containers to minimise the risk of breakage by using break resistant materials. This includes glass vials provided in specially designed outer containers, or glass vials over-wrapped in plastic.

Since different types of packaging are available, we compared unprotected glass vials with glass vials over-wrapped in plastic and glass vials protected by outer containers under defined conditions. The unprotected glass vials were tested to define the risk of breakage in general, while the protected vials were compared with regard to the extent of protection against breakage.

Methods
The tests were performed by using a drop table for testing the impact strength of the various pack-

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### Vertical shock tests with safety packaging materials for cytotoxic drugs

By Wolfgang Teichmann

Cytotoxic drugs are essential in the treatment of cancer, but they are also potentially hazardous substances, that must be kept safely 24 hours-a-day for the protection of those who work with them. The carcinogenic, mutagenic and teratogenic potential of such drugs represent a serious risk to the health of the people involved in the production, preparation and use of these substances.

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Since different types of packaging are available, we compared unprotected glass vials with glass vials over-wrapped in plastic and glass vials protected by outer containers under defined conditions. The unprotected glass vials were tested to define the risk of breakage in general, while the protected vials were compared with regard to the extent of protection against breakage.

### Results

The tests with increased drop heights revealed that Product A (outer container) showed the best results for both pack sizes (10 mL and 100 mL). The average fracture drop height is summarised in Figure 2.
The outer container of Product A showed an average drop height of 336 cm (10 mL) and 186 cm (100 mL) respectively. This data clearly show that Product A offers the best protection against breakage, even under extreme stress conditions due to multiple testing.

The tests with constant drop heights showed comparable results. Product A (outer container) provided the best protection against breakage. The average failure rates (% of broken vials) are summarised in Figure 3.

**Conclusion**

Based on the results of unprotected glass vials the usage of products offering additional safety packaging materials is highly advisable. With regard to the protection against breakage, systems using outer containers offer higher safety for the user compared to products with an over-wrapped plastic foil – even with a reinforced bottom.

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**References**


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Important advances in haematology

The 49th American Society of Hematology (ASH) Annual Meeting was held in Atlanta, 8-11 December 2007. Some of the most important substance-related advances are briefly reported below.

The 49th ASH Annual Meeting was attended by 25,000 experts in haematology and oncology. They discussed recent advances in therapies of leukaemias and lymphomas, control of thrombosis and other coagulatory complications, severe infections, autoimmune diseases and genetic aberrations in haematological diseases.

The atmosphere at the congress was, in general, very positive, as a lot of really innovative substances have entered phase II/III trials. If trials continue to be encouraging, they will significantly improve outcome in life threatening diseases with, until now, unfavourable prognosis. At last we are also experiencing significant advances for the elderly, the large majority of cancer patients, as newer anticancer agents are less toxic and can be given orally.

On the other hand, many physicians and pharmacists are increasingly irritated by the pricing policy of the pharmaceutical industry. It is an increasing problem in several European countries that economic restrictions do not allow prescribing of innovative substances to every patient in need. Whether this problem can be solved by rationing within the health system or by price reductions will be a subject of important public discussion in the future.

90Y-ibritumomab tiuxetan in follicular non-Hodgkin lymphoma
90Y-ibritumomab tiuxetan is an anti-lymphoma antibody coupled to a radioactive isotope. In a phase III randomised trial 414 patients with advanced follicular non-Hodgkin lymphoma responding to first-line chemotherapy and with (minimal) residual disease were treated with this form of radioimmunotherapy (one single infusion). After completing induction therapy patients received either 90Y-ibritumomab (Rituximab on day -7 and day 0, followed by 90Y-ibritumomab on day 0) or no further treatment. The median progression-free survival increased from 13.5 months (controls) to 37 months in the 90Y-ibritumomab group (p < 0.0001). For patient subgroups in partial remission after induction therapy the respective numbers were 6.3 months vs. 29.7 months, for patients in complete remission 29.9 months vs. 54.6 months. Toxicity was mostly haematological.

Thus, 90Y-ibritumomab prolongs progression-free survival by about two years in advanced follicular non-Hodgkin lymphoma in first remission (Hagenbeek A, et al. The Netherlands/multinational).

Imatinib in acute lymphoblastic leukaemia
Five cohorts of children with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia received imatinib (340 mg/m²) for a different number of days (cohort 1: 42 days; cohort 2: 63 days; cohort 3: 84 days; cohort 4: 126 days; cohort 5: 280 days). Imatinib was combined with standard chemotherapy with or without bone marrow transplantation. Increasing imatinib exposure improved early event-free survival at one year (cohorts 1 and 2: 70.6%; cohort 3 and 4: 90.9%; cohort 5: 95.3%). Whether this will result in significant improvements in long-term survival is subject to further investigation (Schultz KR, et al. USA).

Dasatinib in chronic myelogenous leukaemia
Three hundred and eighty-seven patients with chronic-phrase chronic myelogenous leukaemia resistant or intolerant to imatinib were given dasatinib (70 mg twice daily, continuously). After a median follow-up of 15.2 months, 96% of the patients were still alive (progression-free: 90%), 91% showed a complete haematological remission. A major cytogenetic response was attained in 59%, complete cytogenetic response in 49%. Dasatinib was well tolerated (Stone RM, et al. USA/multinational).

Lenalidomide in multiple myeloma
The Eastern Cooperative Oncology Group (ECOG) presented a 2-armed randomised phase III trial in 445 patients with newly-diagnosed multiple myeloma, comparing lenalidomide (25 mg/day PO day 1-21 every 28 days) plus low-dose dexamethasone (40 mg days 1, 8, 15 and 22 PO every 28 days) with lenalidomide plus high-dose (standard-dose) dexamethasone (40 mg days 1-4, 9-12, 17-20 PO every 28 days), 2-year survival was better in the low-dose arm (87% vs. 75%). The excellent results of lenalidomide in patients with multiple myeloma seem to be improved by lower than standard-doses of dexamethasone. This effect may be due to fewer adverse drug effects and to an enhanced action of lenalidomide when the immune system is less compromised (Rajkumar SV, et al. USA).

Deferasirox in sickle cell disease
In sickle cell disease, iron overload of the kidneys and the
liver has to be removed. In a 4-year extension trial the long-term, the efficacy and safety of deferasirox were evaluated, after a previous study of deferasirox compared to deferoxamine had shown similar efficacy of both substances. Deferasirox, which can be administered orally (while deferoxamine has to be given subcutaneously) proved to be safe and effective, with most adverse effects such as vomiting, nausea, diarrhoea and skin rash being mild.

**Immunochemotherapy in mantle cell lymphoma**

Until now, mantle cell lymphoma has been considered incurable. In an unrandomised phase II trial by the Nordic Lymphoma Group, 159 previously untreated patients <66 years of age received intense immunochemotherapy with in vivo purged stem cell support. After six cycles of therapy with alternating cycles of Rituximab + maxi-CHOP and Rituximab + high-dose Ara-C, responders received BEAM/BEAC (BCNU, etoposide, cytarabine, melphalan/cyclophosphamide) with stem cell support. Ninety-six per cent of the patients responded to induction therapy (complete remission 55%, partial remission 42%). Five-year event-free survival was 63%, overall survival 74%. There were six treatment-related deaths. Of the 144 responders who completed treatment, 72% were disease-free at five years. This demonstration of long event-free survival indicates for the first time that intensive immunochemotherapy plus stem cell support may cure MCL (Geisler CH, et al. Denmark/Scandinavia).

**Azacitidine in myelodysplastic syndrome**

Azacitidine, a hypomethylating agent (75 mg/m² days 1-7, every 28 days), was compared with low-dose Ara-C (20 mg/m² days 1-14, every 28 days) in 358 patients with high-risk myelodysplastic syndrome. Azacitidine prolonged overall survival by 9.4 months compared with Ara-C (24.4 months vs. 15 months). Azacitidine was well tolerated by the mostly elderly patients in the study. Azacitidine may now be considered as first-line treatment for high-risk myelodysplastic syndrome (Fenaux P, et al. France).

**Romiplostim (AMG 531) in immune thrombocytopenic purpura**

Romiplostim, a novel “peptibody”, enhances platelet production by stimulating the thrombopoietin receptor. In a randomised double-blind phase III study pretreated and splenectomised patients with chronic immune thrombocytopenic purpura with extremely low platelet counts (mean baseline platelet count 14.7 x 10⁹/L) were given romiplostim (1 μg / kg weekly subcutaneously for 24 weeks) or placebo.

In the romiplostim group 78.6% showed a platelet response (target platelet count 50-200 x 10⁹/L), in 38.1% the response was durable (at least six weeks). There was no enhancement in platelet counts in the placebo group. Of the 42 patients treated with romiplostim, two (4.8%) experienced myelofibrosis as a severe side effect (Gernsheimer T, et al. USA).

**Oblimersen in chronic lymphocytic leukaemia**

Oblimersen decreases production of Bcl-2 (a protein that makes cancer cells live longer) and enhances the activity of fludarabine and cyclophosphamide (FC). In a 2-armed phase III trial on patients with relapsed or refractory chronic lymphocytic leukaemia, standard treatment with FC (25 mg/m²/d and 250 mg/m² x 3 days, respectively) was compared with FC combined with oblimersen (3 mg/kg/d x 7 days, beginning 4 days before FC). The complete response rate was significantly increased by adding oblimersen to FC (17% vs. 7%). The duration of complete response was also longer in the oblimersen arm. Oblimersen-treated patients survived significantly longer (Table 1) while not experiencing higher toxicity (O’Brien S, et al. USA).

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**Table 1: Survival of patients with relapsed or refractory CLL with and without oblimersen**

<table>
<thead>
<tr>
<th>Patients surviving</th>
<th>FC (n = 121)</th>
<th>FC + oblimersen (n = 120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 year</td>
<td>8</td>
<td>20</td>
<td>0.010</td>
</tr>
<tr>
<td>At least 2 years</td>
<td>8</td>
<td>17</td>
<td>0.060</td>
</tr>
<tr>
<td>At least 3 years</td>
<td>4</td>
<td>16</td>
<td>0.005</td>
</tr>
<tr>
<td>At least 4 years</td>
<td>2</td>
<td>12</td>
<td>0.006</td>
</tr>
</tbody>
</table>

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ASCO 2008 congress: many new drugs against advanced cancer — Professor Günther J Wiedemann, MD, PhD; Professor Wolfgang Wagner, MD, PhD

Quite simply, the biggest cancer meeting in the world: more than 30,000 physicians, more than 4,300 oral and poster presentations. A dedicated visitor would probably have walked more than 10 miles over four days traversing the length and breadth of the vast McCormick Place congress centre in Chicago.

The press office selected no more than 12 studies out of 4,300 for their official on-site press coverage of the 44th annual meeting of the American Society for Clinical Oncology (ASCO). These selected studies are then bounced around the world with the help of television and newspapers. This information may be important and interesting but some of the work of thousands of other oncologists will go unnoticed at the same time. A thorough reflection, a controversial discussion and an appropriate evaluation of the data presented are hardly possible within the framework of the world’s biggest cancer congress. This is exactly why post-ASCO meetings and reviews of the results of the most important studies are vital.

This year’s ASCO saw targeted cancer therapies as the focus of interest. There are many new and promising substances that can be used for people with difficult-to-treat disease. They will even find a role in the treatment of older persons, who represent the majority of cancer patients.

Pemetrexed prolongs time to progression in NSCLC

Until now maintenance chemotherapy has not been proven to be of value for lung cancer patients. Pemetrexed is currently approved for treating non-small cell lung cancer (NSCLC) that has progressed despite previous chemotherapy.

In this double-blind multicentre phase III trial 663 patients with stage IIIB/IV NSCLC were randomised to receive either pemetrexed (Alimta) (500 mg/m²) or placebo as a maintenance therapy until progression after successful treatment with four cycles of a platinum-based induction chemotherapy. Progression-free survival was longer in patients who received pemetrexed compared to patients on placebo (4.3 months vs. 2.6 months, p<0.00001). Response was best in non-squamous cancers. Data on overall survival (13 months vs. 10.2 months) are preliminary. Grade 3-4 anaemia occurred more often with pemetrexed (4.5% vs. 1.4%). Abstract #8011 Ciuleanu T, et al.

Vitamin D deficiency associated with metastasis and poor outcome

Vitamin D is vital for regulation of many aspects of cellular growth and differentiation. Low levels have been linked to increased breast cancer risk. This study examined the relationship between vitamin D levels in blood samples and the incidence of metastases and overall survival in 512 women newly diagnosed with breast cancer.

Vitamin D levels were deficient (<50 nmol/L) in 37.5% of women and adequate (>72 nmol/L) in only 24%. Low levels were associated with premenopausal status, high body mass index, high insulin and high tumour grade. After a median follow-up of nearly 12 years metastasis-free survival was significantly worse in women with deficient (versus adequate) vitamin D levels (hazard ratio HR 1.94, p = 0.02) as was overall survival (hazard ratio HR 1.73, p = 0.02). Further studies are needed before any recommendation of vitamin D supplementation for women with newly diagnosed breast cancer. Abstract #511 Goodwin PJ, et al.

Reduced risk of relapse in early endocrine-responsive breast cancer

It is known that zoledronic acid (Zometa) can reduce therapy-induced bone loss. Preclinical research suggested that the drug might also have an anticancer effect. A large clinical trial has now shown that the antitumour properties of adjuvant zoledronic acid improve outcome beyond the effect of endocrine therapy alone.

One thousand eight hundred and one premenopausal women with hormone-responsive breast cancer were randomised to...
Oncogene determines response to treatment

Only patients with wild-type KRAS status will benefit from first-line treatment with cetuximab for metastatic colorectal cancer. This is the conclusion of the first randomised study to compare the effectiveness of adding cetuximab to FOLFIRI (folinic acid, 5-FU, irinotecan) as part of first-line treatment stratified by KRAS mutation status (wild-type (wt) versus mutation (mt)).

KRAS mt were detected in 35.6% of patients. A significant difference in favour of cetuximab was seen in KRAS wt patients for progression-free survival (hazard ratio HR 0.68, p = 0.0167), and best overall response (59.3% for cetuximab plus FOLFIRI vs. 43.2% for FOLFIRI alone, p = 0.0025). Patients with KRAS mt status showed no significant differences between treatment groups. This shows the predictive value of KRAS mutation status for treatment with FOLFIRI plus cetuximab in the first-line treatment of metastatic colorectal cancer. Patients with KRAS mt status could not be shown to benefit from cetuximab treatment.

Abstract #2 Van Cutsem E, et al.

Single dose carboplatin in early seminoma

This comparison of adjuvant radiotherapy (the current standard treatment) with a single dose of carboplatin in stage I seminoma represents the 6.5 years follow-up of a study originally presented at ASCO 2004. This trial confirms the non-inferiority of single dose carboplatin in terms of relapse-free survival and a reduced risk of secondary germ cell tumours in the carboplatin group, thus allowing a choice between therapies according to the patient’s personal preference.

After surgery 904 patients were treated with radiotherapy while 573 patients received one infusion of carboplatin. Relapse-free survival after five years was achieved in 95% with chemotherapy and in 96% with radiotherapy. After 6.5 years of follow-up there was a significant difference in the rate of new germ cell cancers in the contralateral testicle (2 on chemotherapy, 15 on radiotherapy; hazard ratio HR 0.22). Side effects in both treatment groups were low, although patients treated with radiotherapy reported fatigue more often (24% vs. 7%).

Abstract #1 Oliver RT, et al.

Adjuvant gemcitabine more than doubles survival in early pancreatic cancer

The prognosis for patients with pancreatic cancer is poor even after curatively intended resection. Until now gemcitabine (Gemzar) has been the standard in advanced pancreatic cancer, with the role of adjuvant chemotherapy still under discussion. This is the first large-scale phase III trial to show a benefit for any adjuvant chemotherapy in early pancreatic cancer.

The final results of this large multicentre phase III trial including 354 patients showed that adjuvant gemcitabine for six months not only improves disease-free survival but also overall survival after five years. Disease-free survival after five years was 16% in the gemcitabine group as compared with 6.5% in the observation group. Overall survival was 21% (gemcitabine) vs. 9% (observation).

Abstract #LBA 4504 Neuhaus P, et al.

Oral adjuvant chemotherapy with capecitabine is inferior

Older cancer patients often suffer from comorbidities resulting in more severe side effects of chemotherapy. This trial compared the efficacy of an oral, possibly better tolerable chemotherapy regimen (capecitabine, Xeloda) with standard chemotherapy (cyclophosphamide, methotrexate and 5-FU (CMF) or cyclophosphamide, doxorubicin (AC)) in patients aged 65 or older in an adjuvant setting in older women with early-stage breast cancer.

Six hundred and thirty-three patients were randomised to receive capecitabine versus CMF or AC (per physician choice). After a median follow-up of 2.4 years patients in the capecitabine arm were 2.4 times more likely to suffer a relapse and 2.1 times more likely to die than those receiving standard treatment. Toxicity was moderate with more myelosuppression on standard therapy, more hand-foot syndrome and two drug-related deaths on capecitabine.

Abstract #507 Muss HB, et al.

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**Introduction**

Positron emission tomography (PET) is a nuclear medicine technique that measures total tissue radioactivity concentrations derived from a radiolabelled compound (tracer) administered to an individual. By taking blood samples in parallel, complete radioactivity concentration-time curves are obtained in both blood and, for example, brain tissue in each individual. Consequently, parameters describing the influx and efflux between the vascular space and the different cells can be estimated using this technique.

The principle of PET

One of the attractions of PET is the non-invasive monitoring of local tissue radioactivity concentrations within living tissues. The exclusiveness of the method lies in the fact that it not only allows assessment of the delivery of compounds to tissues but also enables the study of cellular and molecular targets.

The principle of PET is based on the physical properties of certain radionuclides that, when decaying, emit a positron. Positrons are particles with a mass equal to that of electrons, but with a positive charge. These particles rapidly lose energy in repeated elastic collisions with electrons in the surrounding tissue and each positron is eventually annihilated along with one electron (Figure 1). Two high-energy photons, which are created as a result of this process, thus leave the site of annihilation in opposite directions.

The PET scanner is equipped with a large number of scintillation detectors arranged in a ring surrounding the object of interest. At the moment of annihilation, two photons of equal energy are detected at the same time and the event is stored in a dedicated data array called a sinogram. Typically, many millions of these coincidences are stored during a PET scan. Coincidences are collected for a finite amount of time, a time frame ranging from a few seconds up to several minutes. Dynamic PET is a term used when several time frames are collected from the same area of the body to track changes in radioactivity concentration over time. The completed sinogram is then converted into a three dimensional data array in a process called image reconstruction. Each data entry in this data array contains the actual radioactivity concentration of a certain portion of the body within the specified time frame.

The three-dimensional image array can be viewed as a stack of tomographic slices on a computer display with colour codes for the radioactivity concentration at a certain time. The dynamic PET data are processed further using dedicated computer software, when kinetic information is required. Regions of interest are delineated within the tissue and data resembling the changes of radioactivity concentration over time are extracted.

Positron-emitting isotopes such as $^{11}$C-carbon, $^{13}$N-nitrogen and $^{15}$O-oxygen are available. These atoms are the building blocks of all living matter and substitution of a stable isotope by the positron-emitting equivalent enables us to track endogenous compounds as well as drugs. Functional imaging evaluates processes occurring at the cellular or tissue/organ level: physiological, e.g. transport carrier systems; molecular, e.g. receptor binding; or biochemical, e.g. enzymatic activity.

**Methodological considerations**

The design of a successful imaging probe is critical as it has the potential to result in a bottleneck in the work [1].
Several aspects need to be considered before performing a PET experiment to obtain quantitative measurements.

From the viewpoint of radiochemistry, the half-life of the positron-emitting isotope must be chosen to match the time scale of the process being probed. The chemists must also be able to synthesise the tracer rapidly, because of the short half-lives of most positron-emitting atoms. Typically one molecule out of 1,700 to 34,000 is radio-labelled with $^{11}$C. In most applications, the tracer dose, i.e. the sum of the labelled and unlabelled molecules, introduced into the system is assumed to be negligible in that it does not affect or perturb the system by its presence. Therefore it is important that the candidate probe can be labelled with as high an amount of radioactivity per amount of probe substance (specific radioactivity) as possible. This means that a low mass of the probe can be administered and still give a sufficiently great radioactivity signal.

The ratio of the target to non-target location of the radiotracer within the tissue is critical. The higher the ratio, the more likely it is that the signal can be used to measure changes in available specific binding sites, e.g. receptors on cells causing disease. Non-specific binding is one crucial factor that affects the target to non-target ratios. The ideal reference region should have similar free and non-specific binding properties to those in regions with specific binding. This is, however, dependent on the tracer and will vary with the characteristics of the proteins in the tissue that non-specifically bind the radio-ligand.

Finally, the affinity of a radiotracer should be based on a balance between the requirement to take measurements with a signal-to-noise ratio as high as possible, and the ability to obtain the measurements in a reasonable period of time.

**Applications of PET in oncology**

PET is used to quantify the kinetics of biological processes in the living tissue in health and in disease states. By proper choice of radiotracer it has been possible to quantify blood flow and volume, tissue pH, metabolism rate of glucose, enzyme location and activity, neurotransmitter synthesis as well as receptor location, affinity and selectivity. Recently, PET has also had a large impact in drug discovery, as it is able to quantify duration as well as selectivity of the receptor binding. PET has found application in studies of disease processes, but also in diagnosis, prognosis and treatment effects in disease. The largest impact has been in clinical oncology where PET investigations are now routine in certain cancer diagnoses and are also reimbursed by the insurance system. In other indications, PET is mostly used as a prominent research tool.

In clinical oncology and as a whole, 6-fluoro-deoxyglucose (FDG) is far the most used radiotracer. FDG is taken up by the cells after intravenous administration but catabolism is blocked in the first hexokinase step. This means accumulation of the radioactivity in the cell which by kinetic calculations is converted to the rate of glucose metabolism. This is an accurate measure and highly useful in many applications. Sometimes the radioactivity in the tumour is similar to that in surrounding normal tissue, which makes delineation more difficult.

Specific radiotracers for PET in oncology have also been developed. DNA bases, e.g. thymidine, can be labelled by several radionuclides, then neurotransmitter synthesis can be measured in endocrine tumours. To examine brain tumours the amino acid methionine is labelled with $^{11}$C. A typical example of radiotracer development is shown in prostate cancer below.

**PET radiolabelled markers of prostate cancer**

Prostate cancer is the most frequent cancer found in men. The tumour is usually slow growing and most do not give symptoms. It is estimated that 15–30% of men over 50 have histological evidence of cancer in the prostate rising to 60–70% by the age of 80, but only one in 25 men (4%) will die from this disease [1]. A method of detecting only the malignant would thus be very valuable to prevent early death from the disease. One feasible method would be PET and several alternatives are at hand.

FDG. The standard oncology test, FDG PET scanning, has shown lim-
ited success in detecting tumours in the prostate. The reason is a slowly growing tumour, using little energy, so little contrast with the surrounding tissue. FDG PET is not able to differentiate a carcinoma or an adenoma and cannot adequately discover a relapse after complete prostectomy.

**Methionine.** Significantly more tumours are identified using PET with $^{11}$C methionine as radiotracer. However $^{11}$C methionine is also taken up by dormant tumours, clearly lowering the validity of PET scanning.  

**Acetate** has been used in prostate cancer with PET and showed higher detection frequency than FDG PET (Figure 2). $^{11}$C-acetate can act as a probe of tissue metabolism through entry into metabolic pathways as mediated by acetyl-coenzyme A. However the uptake of $^{11}$C-acetate is age dependant with a risk of over-diagnosis in people older than 50 years. Further, the uptake of $^{11}$C-acetate is low both in tumour and normal tissue with some overlap as well.  

**Choline** is incorporated in cell membranes and radio-labelling of choline with $^{11}$C or $^{18}$F and PET has shown promising detection of the primary tumour as well as lymph node metastases. Considerably more tumours have been detected compared to FDG PET. This tracer awaits large clinical studies before becoming the first choice for prostate cancer diagnosis. **Monoclonal antibodies** are primarily developed for diagnosis using Single Photon Emission Computer Tomography (SPECT) but also for therapy. The method can be extended to PET after choosing a suitable radionuclide.  

**Endothelial growth factor** can also be used with SPECT for diagnosis of cancer and has also been applied with PET with $^{68}$Gallium as radionuclide chelating to the growth factor.

In conclusion, several alternative methods using different radiotracers have been developed for prostate cancer as an example. Development of selective tracers for specific process in tumour tissue is ongoing.

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**Reference**  

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**Lipoplatin: First line treatment for NSCLC**

Tumor targeted  
Liposomal cisplatin nanoparticle  
Extravasates to tumors  
Low neuro- & nephro-toxicities

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Regulon A.E.  
Afxentiou 7,  
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Clinical case study: unexpected toxicities in colorectal cancer treatment

With a good knowledge of gene polymorphisms and modern therapeutic options a hospital pharmacist can suggest the reason for toxicity and help with its treatment. A knowledge of KRAS mutation status could inform the choice of whether or not to proceed with treatment.

Case history
A man aged 66 years, 82 kg, 175 cm, was treated for a node-positive colon carcinoma, classified T3N1M0 (3b or Dukes C). After radical colectomy he received the FOLFOX4 adjuvant regimen. During the sixth course he suffered from grade 2 peripheral neuropathy and grade 3 neutropenia. The dose of oxaliplatin was reduced to 75 mg/m². Three years later without any problems, an abdominal scan revealed disease progression. It was decided to include the patient in the CRYSTAL trial in the arm including FOLFIRI plus cetuximab. After the first course, the patient developed severe neutropenia (0.5 x 10⁹/L) and severe diarrhoea. The oncology pharmacist was asked to explain these unexpected levels of toxicity and to suggest solutions.

Staging and initial treatment
Our patient was classified 3b corresponding to invasion through the muscularis propia into nonperitonealised perimuscular tissue <2 cm (T3), 2 lymph nodes (N1) and no simultaneous distant metastasis (M0). The regional lymph node number is essential to predict survival. The TNM stages for nodes are N0 for no nodal metastasis, N1 for 1-3 nodes and N2 for >3 nodes. According to Le Voyer et al. [1], the 5-year life expectancy for our patient was 64.1% but it would be only 44.3% for stage N2 (and only 8.1% for stage M1).

Initial surgery is an essential part of colorectal cancer (CRC) treatment. For stages I and II it is enough to be curative. However, for patients with node-positive resectable colon cancer, the combination of 5-FU plus leucovorin improves the disease-free survival (DFS) as well as the overall survival (OS).

Our patient was treated by an R0 colectomy (total removal of all cancerous tissues with a safe margin of 2 cm). He received adjuvant chemotherapy since he was N1. Combination FOLFOX4 was chosen rather than a single agent regimen (oxaliplatin 85 mg/m² as a 2-hour IV infusion added to classical LV5FU2). The MOSAIC study which compared FOLFOX4 vs LVFU2 in patients with stage II/III colon cancer, demonstrated a 4-year DFS advantage for combination therapy. For all stages, the DFS was 78.7% for FOLFOX4 vs. 73.3%; hazard ratio 0.76 [0.64-0.86]; p = 0.0008. For stage III as in our patient the DFS was 72.8% vs. 65.8%, hazard ratio 0.75 [0.62-0.90]; p<0.002, corresponding to a 25% risk reduction [2].

Discussion
Our patient experienced peripheral neuropathy and progressive neutropenia. Neurosensorial toxicity is common with oxaliplatin. In the MOSAIC study, 48.2% of patients suffered from grade 1 neuropathy and 12.4% from grade 3. Fortunately, neuropathies are usually reversible and do not require dose reduction. However, other side effects such as grade 4 diarrhoea or grades 3-4 neutropenia (<1 x 10⁹/L) or thrombopenia (5 x 10⁹/L) require dose reduction.

Several studies have suggested that targeted therapies acting on vascular endothelial growth factor VEGF, e.g. bevacizumab, could be useful in the treatment of advanced CRC [3]. Moreover, drugs acting on endothelial growth factor receptors (EGFR) such as cetuximab (Erbitux) could be also efficient [4]. Thus, our patient was enrolled in the randomised CRYSTAL trial which tested the combination of cetuximab with the FOLFIRI regimen in 1198 patients suffering from advanced CRC. This regimen includes irinotecan 180 mg/m² in combination with LV5FU2 plus cetuximab 250 mg/m². Cetuximab is an anti-angiogenic monoclonal antibody that acts by blockade of EGFR. Concerning our patient, preliminary results of the CRYSTAL study demonstrated a slight but significant improvement of time to progression (TTP) with the cetuximab
Our patient developed grade 3 skin toxicity, which was considered a good predictive marker as previously discussed, but also severe neutropenia (0.5 x 10^9/L) and diarrhoea. Myelosuppression inducing neutropenia, anaemia and thrombocytopenia are common but not usually severe, except for patients with a particular phenotype for metabolism. This is because irinotecan is a prodrug that is transformed by carboxylesterases into its active metabolite, SN38, which stabilises topoisomerase I. This metabolite can be inactivated by glucuronono-conjugation by the hepatic enzyme UGT1A1 (uridine diphosphate-glucuronyl transferase) and excreted by the biliary and renal route. Expression of enzymatic activity depends on the UGT1A1*28 gene which exhibits more than 25 different polymorphisms. About 50% of the population have the wild type (6/6 TA unit), 40% the single-mutated phenotype 6/7 and 10% the homozygous mutation 7/7 (Gilbert’s disease). This bi-allelic mutation strongly decreases the glucuronono-conjugation of SN38. Indeed, it has been demonstrated that the AUC of SN38 and the subsequent haematological toxicity correlates with the polymorphism of UGT1A1, the bi-allelic mutation inducing more toxicity [7]. The data in this case indicated that UGT1A1*28 polymorphism may be a key determinant for predicting irinotecan-induced severe toxicity without affecting treatment outcome for patients with metastatic CRC.

The pharmacist’s suggestions
The oncology pharmacist suggested UGT1A1*28 gene mutation to explain the unexpected neutropenia. Upon genotyping, our patient showed a 7/7 mutation, demonstrating that he suffers from Gilbert’s disease. The use of a neutrophilic growth factor could be suggested. A determination of the AUC of the metabolite SN38 from the plasma levels could be suggested. However, this determination is not currently feasible in most hospitals. Moreover, there is no well established dose adjustment to control SN38 plasmatic levels or AUC and activity or toxicity. Practically, a half dose reduction could be suggested plus administration of a neutrophil growth factor. Since diarrhoea was severe, the pharmacist also suggested appropriate IV hydration and electrolyte supplementation to prevent hypovolaemia and shock. Besides classical drug management of diarrhoea (loperamide, atropine, codeine), the pharmacist suggested octreotide starting at 0.1 mg SC t.i.d. (may be increased to 1.8 mg/day). Finally, the pharmacist suggested the determination of the KRAS mutation status since a good correlation exists between treatment failure and mutation of this key gene. In CRC, 30-40% of patients have the mutated genotype. Indeed, for example, in patients in 3rd and 4th lines of treatment ( cetuximab + irinotecan), OS was 44.7 weeks for non-mutated KRAS versus 27.3 weeks for mutated KRAS (p = 0.003) [8].

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References
A standard operating procedure is brought into use. The pharma-validation testing of every aspect of production before a new one vial! Therefore six entire sequences should be reserved for tests before a product is on its way and the whole batch is often difficulties are enormous. Ten minutes may be available for QC a cyclotron needed to generate the isotopes, the technical diff-

with isotope half-lives of between 2 minutes and 1.8 hours and patients are at minimum risk from the procedure. However, The very short half-lives of positron emitters are desirable, so 

quality control has to check the radionuclide identity and purity, prepare the reagent by getting the isotope produced to react normally with an endogenous compound, and then purify it, do all the normal QC checks as well as a radioactivity check, and get the radiopharmaceutical to the patient, all within a very short time frame and with minimal exposure of the staff to radiation.

Practical problem solving
The research aspect is most satisfying to some. An Edinburgh radiopharmacy was asked to supply $^{99m}$Tc albumin nanocol-

loid to the breast surgery theatre for intra-operative sentinel node localisation. As the members of staff in this theatre were unfamiliar with handling radioactive material, supplying the product in unit dose syringes seemed the most appropriate means of minimising their radiation exposure. Measurements were made to validate a syringe as a suitable container: adsorp-

tion of the radiocolloid to the syringe, labelling efficiency by thin-layer chromatography and particle size by Nuclepore filtra-

tion and photon correlation spectroscopy. This radiopharmaceut-

tical is now supplied routinely [1].

Sometimes the question is why do things go wrong. Routine measurements of the radiochemical purity of the renal imaging agent $^{99m}$Tc-MAG$_3$ revealed occasional unacceptably high levels of a lipophilic impurity. The reason for this was traced to a compound that leached from the rubber tips of syringes used in reconstitution of MAG$_3$ kits. Elimination of the problem was achieved by using two-piece syringes [2]. Occasional low radiochemical purity has also been observed when MAG$_3$ kits are reconstituted with sodium chloride injection from plastic ampoules. Investigation of this phenomenon revealed that the ampoules had been exposed to light. The problem is over-

come if either plastic ampoules are protected from light or sodium chloride injection from glass containers is used [3].

References
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