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Our capability needs a goal – patients need our competence

Klaus Meier
Editor-in-Chief
President of ESOP

EJOP

For more than 20 years pharmacists have gained a good reputation in preparing cytotoxic drugs. They had to grow their knowledge not only about the drugs themselves but also to start to understand more about therapies and medical decision making.

It was only a matter of time before pharmacists felt the need to share their experience at a national and international level in order to raise their educational level. ESOP took early steps alongside the ECCO meeting in 1999 in Vienna, Austria, and ten years later it has become an established part of the European CanCer Organisation. At the ECCO conference 2009 in Berlin, Germany, it will be presenting in several lectures and sessions its understanding of how oncology pharmacy can best support the treatment of cancer patients. This demonstrates the increasing importance of good education.

In the perspective of history, ten years appear like a blink of an eye, but for those who have been responsible for progress it is a long way. Three conferences were held in Luxembourg in 2001, 2004 and 2008 to discuss quality standards in oncology pharmacy service, gradually agreeing a basis for common understanding and support from 22 countries. Good news is the formation of a committee with delegates from France, Germany, The Netherlands and UK. Its mandate is to harmonise our understanding of continuing education. The sooner oncology pharmacy adopts a common position, the better we can contribute to the development of continuing medical education in Europe (see page 6). Read about recent QuapoS discussions on pages 4-6 and a presentation of the developing UK system on pages 18-19.

But we must never forget the individual responsibility of oncology pharmacists for reflection and self-auditing in daily work. Patients are asking for support and are looking for a well equipped pharmacist to partner other healthcare providers. So take advantage of the continuing education articles in this issue: latest treatment for renal cell carcinoma pages 8-12 and ASH 2008 conference report pages 22-23.

When these days physicians are discussing the increasing efficacy of interdisciplinary work, then we should realise that in 95% of these discussions they are talking about the collaboration of internal medicine and surgery. The role of nurses and even less that of pharmacists is generally not included in this word "interdisciplinary".

That is why we are presenting ourselves as a part of the "multi-professional team". The radiology feature in this issue illustrates the added value a pharmacist can bring, pages 14-17. The use of this new term will grow because of changes in therapy, a fact not yet fully recognised by most physicians.

The chance of surviving cancer is increasing all the time. The methods of treatment are changing from intermittent IV to continuous oral regimens. The safe and effective use of orally administered targeted treatments for cancer also has to be learned by pharmacists. The profession needs to understand how these therapies are used, what toxicity to expect and how to manage it. We have to learn, in words of the BOPA's past chairman, Mr Geoff Sanders, "how services can be developed to accommodate this expanding section of the oncological armoury."

To do this we have to change too. In the past in Germany, although certified community pharmacies are allowed to prepare IV drugs, these drugs have been administered in hospitals only. Several countries have rules stating that IV treatment has to be prepared in hospital pharmacies. But how will the situation change if oral drugs start to become the norm and the great problem of non-compliance provokes bad treatment results? Dr Lukasz Lapinski outlines the compliance problem on page 13. Worse still, the wrong medicine taken daily could result in treatment breaks and sudden death.

This situation can only be avoided through the assistance of community pharmacists, who will have the chance to make all the necessary information available directly to their patients and take on the whole gamut of treatment with medicines. This will not come about by itself. National guidance has to be developed and implemented. The oncology pharmacist can initiate this process and can bridge the gap between patient needs and pharmacists' abilities. At the EU level, ESOP welcomes Europa Uomo as a new partner, see pages 19-20.

As early as possible oncology pharmacists need to understand their leading role in organising the best support for patients. Then they will be understood as a supporting pillar in the hall of multi-professionalism.

Pharmaceutical oncology standards in Europe

It is an uphill struggle to get all centres in Europe to treat cancers to the same standard, as the understanding and treatment of these conditions constantly evolves. ESOP, the EU and patient groups are partners in this process and were all represented for this review of the present situation.

The third meeting of QuapoS (Quality Standards for Pharmaceutical Oncology Service), was held in the EU Commission building, Bâtiment Jean Monnet in Luxembourg, 26-27 September 2008. Almost 70 participants attended from 19 countries. The conference theme was "Through the eyes of the patients". The first session of the meeting focused on presentations on this theme and several distinguished guests spoke.

The EU Commissioner for Health and Consumer Protection, Mrs Androulla Vassiliou from Cyprus, told of the devastating effect of cancer on patients, the family and society. The EU Commission has several projects to combat cancer and some of them were discussed:

- Investigation of the difference in cancer rates in regions in Europe
- Action on obesity and initiatives for a better diet
- Smoking information and smoking prophylaxis
- Vaccination, e.g. *Helicobacter pylori* programmes for selected cancers
- Screening programmes for breast, cervix and colorectal cancer
- Information for the public on cancer prevention
- Treatment initiatives with encouragement for drug companies to do research

Professor Louis Denis, Antwerp, Belgium is a professor in surgery but also a cancer patient. He pointed out that almost 40% of patients received wrong or incomplete treatment for their cancer. He concluded that medicines management is an important task for pharmacists. He also presented the initiatives taken by cancer patient organisations to inform, support and encourage cancer patients. He was interested in further collaboration with ESOP to support patients.

Klaus Meier, Germany, President of ESOP, spoke next to describe ESOP's mission and its vision for the future. He also gave details from a survey in Germany of cancer patients' views on pharmaceutical care. The majority of patients need more information and would benefit from information from pharmacists, but few patients realise that this is possible. Complementary and alternative medicines are used by a majority of cancer patients. In Germany more money is spent on complementary treatment than conventional treatment.

The session closed with two scientific lectures. Professor N Schleucher, Hamburg, Germany, questioned whether there is really such a thing as targeted therapy in oncology. Professor Robert Mader from Vienna, Austria talked about pharmacological lessons learned and lessons to be learnt about the interplay between inflammation, angiogenesis and cancer tumours. He concluded that "The complex interaction between biology and pharmacology will bridge the treatment options and validate and help the clinical oncologist to make correct decisions".

In the late afternoon the quality standards of QuapoS were scrutinised in five different workgroups, which continued their work on the second day. Below you will find the most important recommendations of each working group.

Education and training chaired by Hannelore Kreckel, Germany

This workshop focused on the need for continuing education of pharmacists in "Oncology Pharmacy Practice" and the need for an ESOP qualification. The purpose of such certification was seen as the need for other healthcare professionals, authorities and hospital managements to recognise competence.

The knowledge, skills and attitude acquired during a specialisation period should enable pharmacists to work effectively in a multi-professional team. Changes in practice and the concept of life-long learning mean that certification has to be limited to a certain period. A two-step approach including basic and advanced levels should be taken. Basic knowledge includes safe handling, principles of anti-neoplastic therapy, cancer prevention and the promotion of early detection, as well as a knowledge of drugs. This knowledge can be acquired by independent study and demonstrated in a written examination. The advanced level, to achieve an ESOP certificate, may consist of a mandatory and an optional part. The following points were considered to be mandatory: oncology pharmacy practice including care plans, medicines management, drug information, the preparation of guidelines, skill in communication with the patient, teaching and presentation skills. Optional points may include skills such as teamwork or project management, clinical trials in oncology, horizon scanning and research. Education by e-learning programmes, conferences, masterclasses and workshops must be considered to improve skills. It was stated that ESOP certification would not have the same relevance for all countries but would be of special interest for those countries where a national certification programme is not likely to be set up.

Technical aspects chaired by Irena Netikova, Czech Republic and Professor Robert Mader, Austria

The aim of this workshop in oncology pharmacy was to discuss the present status in comparison with QuapoS 3. For every individual technical issue the main question asked was "Do we feel comfortable with the current standards?"

During the workshop a number of important topics for the future were discussed such as: handling compounds with various classes of toxicity (cytotoxics, monoclonal antibodies); drug delivery to the pharmacy (vial contamination/labelling); the current list of drugs carcinogenic, mutagenic or toxic to the reproductive system; aseptic process validation; closed systems; electronic prescriptions, oral medicines and home care. An electronic prescribing system is favoured to reduce errors and improve safety. There was a call for a new chapter in QuapoS: "The patient's point of view". Proper procedures and techniques will guarantee a high quality of anticancer treatment.

The introduction by ESOP of a "yellow hand" with a contact phone number (hotline) to the pharmacy as part of the labelling of ready-to-use solutions for home care was seen to be a significant improvement. There are no standards for information on handling oral formulations at the moment. ESOP is also going to provide patient information to accompany drugs prescribed for home care: what to do with excreta, extravasations and possible incidents. A leaflet is being written to accompany every prescription.

The conclusions reflect the fact, that QuapoS has already established a very high standard for a variety of aspects. We now need these materials to be accepted and implemented with official backing in all European countries. QuapoS' harmonisation of similar guidelines is a long-term goal and improvements will rely on further evidence.

Pharmaceutical care chaired by Kathleen Simons, The Netherlands and Professor Alain Astier, France
The aim of the workshop was to discuss the present status measured against QuapoS 3. Participants thought the starting point must be a definition for oncology pharmaceutical care in Europe. From this base, uniform minimum standards for all European Member States with regard to cytotoxic prescription, patient counselling and prevention of drug events/medication errors can be defined.

Therefore it is important that:
- Oncology pharmacists are full members of the multidisciplinary team managing chemotherapy.
- Oncology pharmacists have full access to all pertinent data to support high level pharmaceutical care.
- European oncology pharmacists strongly support the ECCO recommendation that all chemotherapy should be prescribed according to a previously defined protocol.
- Oncology pharmacists should ensure that chemotherapy prescriptions comply with ESMO standards.
- Oncology pharmacists should assess requirements for patient information.

Another important question was how to raise patient compliance. This could be achieved by a patient-centered approach and advice, together with medicines counselling and lifestyle modifications. Participants drew attention to leaflets that have already been compiled in hospital in Leipzig, Luxembourg and Madrid, Spain.

It was agreed that these goals cannot be achieved in all countries at the same time. Nevertheless, QuapoS has already established a high standard for a variety of aspects.

Quality management chaired by Jeff Koundakjian, UK and Gisela Sprossman Guenther, Germany
Quality management should be incorporated into the standards of QuapoS. Clear standards need to be set and, ideally, these should be achievable, although in some instances they may need to be aspirational. Once the highest standards have been agreed and set, there is a need to arrange constant monitoring to maintain these standards. This will preserve and enhance the ability of the oncology pharmacy staff to meet the needs of cancer patients. A new QuapoS section on Quality Management is required.

Standard Operation Procedures must be kept and readily available for all technical areas of the pharmacy. Completed worksheets must be kept for regular audit. Records must be kept of staff workload and exposure to cytostatic agents, and environmental records and settle plate results must be available. Records of staff absences and accidents may also demonstrate trends that need to be investigated.

Records of adverse incidents and complaints should show what action has been taken, and the result of this action. All procedures and equipment, including computers and software must be validated for accuracy and records kept, including changes to the procedures.

Documentation underpins the audit process. *If it was not documented, it did not happen*.

Research and Development chaired by Professor Per Hartvig-Honoré, Denmark
Oncology pharmacy practice and information should be based on scientific evidence as well as validated experience. Therefore,

A positive spirit was evident at QuapoS 3

research and development in oncology pharmacy is essential for further progress, as in other medical and pharmaceutical sciences. Research must be of high quality and focused on improving cancer treatment, cancer knowledge and improving the patient's situation. The oath "not to hurt" is a leading objective. The subject of the research must have both pharmaceutical and medical relevance, be clearly formulated, well structured and fully documented. Results should be disseminated to the scientific world and to oncology pharmacy. There is a special responsibility to perform research and high quality standards must be secured and validated in all projects. Projects for research and for development of oncology pharmacy are open to all. Expert oncology pharmacists in centres must provide support and supervision for excellent research projects.

In the eyes of patients, the oncology pharmacist is another type of professional, who will inform him about his treatment, managing his treatment as a whole, including other co-morbidities and not only focusing on the cancer. He will give an increased understanding of different entities and the patient will feel a safety and quality in drug prescribing and administration.

Knowledge and competence of pharmaceutical oncology care are essential to keep these values for the patient. Services must be well managed, methods continually reviewed and updated: analyse, plan, implement and validate. Further, scientific studies must be performed. The advantage to the oncology patient of scientific studies is that results are disseminated to other departments and patients, communication is better to patients and among professionals, time saved will be used for more effective treatment and to foster more rational use of resources, e.g. beds, drugs. As a practical exercise, the group planned a multicentre study to test whether "close multidisciplinary medicines management reduces the intensity of nausea and number of emesis episodes in breast cancer patients on chemotherapy". The intention was not that the study should be performed, but that it should encourage other oncology pharmacists to consider doing or joining a study.

ESOP plans

An ESOP delegates meeting was held before the QuapoS meeting to plan the 2009 events. An important forthcoming event is the second part of the Masterclass from 5-7 March 2009 dealing with clinical oncology pharmacy.

All information can be found on www.esop.eu. In September 2009, ECCO 15 will take place in Berlin, Germany. ESOP will organise and participate in several symposia and seminars. This is an opportunity to show ESOP's competence and its ability to support the European CanCer Organisation.

Author
Professor Per Hartvig-Honoré, PharmD, PhD
Secretary of ESOP

ESOP News

The Medical Oncology Status in Europe Survey (MOSES)

ESMO recently promoted medical oncology to members of the European parliament. Advancing this discipline will benefit cancer sufferers.

On 15 October 2008, the European Society of Medical Oncology (ESMO) invited ESOP to a keynote debate titled *Towards Better Cancer Care in Europe* on improving cancer care in Europe. The meeting was attended by members of the European parliament, national experts and representatives from oncology interest groups including patients with cancer. Monika Sonc from Slovenia and I jointly represented ESOP. The Medical Oncology Status in Europe Survey (MOSES) was presented as a good source of information on differences in cancer care around Europe.

Medical oncology is not recognised in the EU in the same way as the other modalities of cancer treatment, surgery and radiotherapy. This is a serious shortcoming and efforts should be made to include experts in this field in the cancer care team. Approval is available at EU level but there are still national problems and obstacles. Education is not uniform in the EU and therefore education in medical oncology may also be lacking. Multidisciplinary teams are not standard throughout Europe but vary with respect to the site of the cancer, as some are built on organ specialists. New treatment is costly and has been estimated at Euros 14,000 a day. It really calls for good sense, analysis and constructive criticism to use the medicines only when indicated. Education, knowledge and experience are "musts" today for medical oncology. Drugs for cancer are the most complex, dangerous and expensive of all treatments and must be managed by the most experienced drug specialists in cancer treatment.

A further topic was cancer care abroad. This is estimated at 1% of total treatment costs. It is a good idea if one country has low capacity in a certain area or if experience and treatment is lacking in the patient's home country. An initiative to inform patients on care abroad was taken. The initiative does not expect to generate a much-increased flow, rather, considerably better possibilities for individual patients. Patients now have the legal right to visit another EU country for treatment.

ESOP will continue to follow the EU initiatives on cancer care and support as far as possible with oncology pharmacy expertise.

Professor Per Hartvig-Honoré, PharmD, PhD

Best use of targeted agents for the treatment of advanced renal cell carcinoma

The advent of targeted therapies has substantially improved the prognosis of patients with metastatic renal cell carcinoma. Clinical outcomes can be optimised by patient education, close patient monitoring, appropriate dosing and prompt adverse event management by a multidisciplinary healthcare team.

Introduction

Renal cell carcinoma (RCC) occurs typically in patients aged 60-70 years, more commonly in men than women, and causes approximately 20,000 deaths annually in Europe [1, 2]. RCC is often asymptomatic until it reaches an advanced stage; approximately 25-30% of patients are diagnosed with metastases [3]. Furthermore, a high proportion of patients who undergo curative nephrectomy for localised RCC go on to develop metastases [3].

Professor Sylvie Négrier MD, PhD

Historically, treatments for metastatic RCC (mRCC) included the cytokine therapies interleukin-2 or interferon alpha (IFN-α), which were associated with limited efficacy and toxicity concerns [3]. Improved understanding of the molecular mechanisms of RCC led to the development of targeted therapies, which now represent the standard care for mRCC.

This article will review clinical efficacy and safety data for the targeted agents currently available for mRCC. It will also discuss practical strategies for optimising treatment outcomes with these agents, with a particular focus on sunitinib malate (Sutent).

Targeted therapies in mRCC

Sunitinib

Sunitinib is an oral, multitargeted receptor tyrosine kinase inhibitor (TKI) that is approved multinationally for the first- and second-line treatment of mRCC [5]. Sunitinib targets vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R), and glial cell line-derived neurotrophic factor receptor (REarranged during Transfection; RET) receptors [5].

In a multicentre phase III trial in mRCC patients [6], first-line sunitinib (50 mg/day for 4 weeks, followed by 2 weeks off treatment in 6-week cycles; Schedule 4/2) was compared with IFN-α (9 million units [MU] subcutaneously three times weekly [t.i.w.]). Sunitinib was associated with median progression-free survival (PFS) more than double that seen with IFN-α (11 months vs. 5 months, respectively) and a superior objective response rate (31% vs. 6% respectively; both $p < 0.000001$) [6]. Median overall survival (OS) was extended beyond two years, the first time that this has been achieved in mRCC trials in the first-line setting (see Table 1) [7]. Further, when the data were censored to exclude patients who had switched from IFN-α to sunitinib therapy, a statistically significant difference in median OS was observed (26.4 months with sunitinib vs. 20.0 months with IFN-α; $p = 0.0362$) [7]. Sunitinib also conferred OS benefits across all Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk groups [8].

In the second-line setting, sunitinib has demonstrated efficacy after cytokine failure, with median OS of 23.9 months and PFS of 8.8 months [9]. It has also shown activity in an expanded-access study in a broad population of patients (N = 4,622) who

Table 1: Efficacy data from phase III randomised clinical trials

Agent	Setting	Median PFS, months	p-value	Median OS, months	p-value
Sunitinib (vs. IFN-α) [6, 7]	First-line	11 (vs. 5.0)	<0.000001	26.4 (vs. 21.8)* 26.4 (vs. 20.0)**	0.051 0.0362
Sorafenib (vs. placebo) [12, 13]	Second-line	5.5 (vs. 2.8)	0.000001	17.8 (vs. 14.3)§	0.0287
Temsirolimus (vs. IFN-α) [18]	First-line§§	5.5 (vs. 3.1)	0.0001	10.9 (vs. 7.3)	0.0069
Bevacizumab plus IFN-α (vs. IFN-α) [20, 21]	First-line	8.5 [21]¥–10.2 [20] (vs. 5.2 [21]¥–5.4 [20])	0.0001	NR	NA

* Final median overall survival data for sunitinib versus interferon alpha (IFN-α) for whole patient population;
** Median overall survival data when patients who had switched from IFN-α to sunitinib therapy were excluded from the analysis [7]
§ Data censored for patients who switched from placebo to sorafenib treatment [3]
§§ Patients classified with poor prognostic risk based on the modified Memorial-Sloan Kettering Cancer Center (MSKCC) prognostic risk criteria [18]
¥ Data reported as time to tumour progression [21]
PFS: progression-free survival; OS: overall survival; IFN-α: interferon alpha; NR: not reported; NA: not applicable

would otherwise have been excluded from clinical trials, including patients with brain metastases [10].

The tolerability profile of sunitinib is discussed later in this article.

As a result of the efficacy observed, the European Association of Urology (EAU) guidelines recommend sunitinib for first-line use in patients with mRCC (Grade A recommendation) [3] and sunitinib is now considered the standard treatment for this condition.

Sorafenib

Sorafenib is an oral, multitargeted TKI that targets VEGFR-2 and -3, PDGFR-β, FLT3, KIT, RET, B-Rad and Raf-1/C-Raf [11].

In a phase III trial in mRCC patients who had failed prior systemic therapy, sorafenib (400 mg twice daily [b.i.d.]) conferred significantly longer median PFS compared with placebo (5.5 vs. 2.8 months; $p < 0.001$; see Table 1) [12]. Median OS was also significantly greater with sorafenib than with placebo when data were censored for patients who had switched from placebo therapy (17.8 vs. 14.3, respectively; $p = 0.0287$; see Table 1) [13]. A phase II study of first-line sorafenib (400–600 mg b.i.d.) versus IFN-α (9 MU t.i.w.) in mRCC showed no significant difference in median PFS between the two agents (5.7 vs. 5.6 months, respectively; $p = 0.504$) [14]. Findings from a sorafenib expanded-access programme were consistent with those seen in the phase III trial [15].

Sorafenib has a manageable tolerability profile, with a low incidence of severe adverse events (AEs) reported in clinical studies [12]. A clinical review comparing sorafenib with sunitinib has suggested similar mechanisms of action for the two agents, with some differences in toxicity profiles [16].

The EAU guidelines recommend sorafenib for the second-line treatment of mRCC (Grade A recommendation) based on phase III trial data [3].

Temsirolimus

Temsirolimus is a mammalian target of rapamycin (mTOR) inhibitor that is approved in Europe for the treatment of patients with poor-risk mRCC [17].

In a randomised phase III study, treatment-naïve patients with poor- and intermediate-risk mRCC (poor-risk patients exhibited 3 of 5 criteria according to the modified MSKCC prognostic classification), received IV temsirolimus (25 mg/week), IFN-α (3 MU t.i.w.) or both agents. In poor-risk patients, median PFS and OS were significantly longer for temsirolimus than for IFN-α monotherapy ($p = 0.0001$ and $p = 0.0069$, respectively; see Table 1) [18]. Grade 3-4 AEs occurred in 67% of poor-risk patients in the temsirolimus arm, versus 78% and 87% in the IFN-α monotherapy and combination therapy arms, respectively. Based on this study, the EAU guidelines recommend temsirolimus as first-line treatment for poor-risk mRCC patients only (Grade A recommendation) [3].

Bevacizumab

Bevacizumab is a humanised monoclonal antibody that targets major VEGF-A isoforms, which is given in combination with IFN-α for the treatment of mRCC [19].

Two randomised phase III studies compared combination treatment with bevacizumab (10 mg/kg every 2 weeks) plus IFN-α2a (9 MU t.i.w.) versus placebo plus IFN-α2a [20, 21]. In both studies, median PFS and objective response rate were superior for bevacizumab/IFN-α2a compared with placebo/IFN-α2a (both $p < 0.0001$; see Table 1) [20, 21]. Median OS has not yet been reached with bevacizumab/IFN-α2a in either study. In the first study, more AE-related treatment discontinuations and serious AEs were reported with bevacizumab/IFN-α2a than with placebo/IFN-α2a (28% vs. 12% and 29% vs. 16%, respectively) [20]. The second study also reported a higher incidence of grade 3-4 AEs with bevacizumab/IFN-·2a (79% vs. 61% with placebo/IFN-α2a) [21].

Combination bevacizumab/IFN-α2a therapy is recommended as an option for the first-line treatment of mRCC in the US National Comprehensive Cancer Network (NCCN) guidelines (category 1 recommendation) [22].

Tolerability of sunitinib

Studies in the first- and second-line settings have reported consistent tolerability with sunitinib, including in the expanded-access study involving more than 4,000 patients [23].

The most common AEs reported with first-line sunitinib in the phase III trial included fatigue, gastrointestinal symptoms, hand-foot syndrome (HFS), hypertension and haematological disturbances [6]. Most AEs were mild-to-moderate in severity and were easily managed, with a low incidence of severe AEs [6]. Long-term data from the expanded-access study reported no new or unexpected long-term toxicities and a low incidence of cardiac disorders [23]. Treatment-emergent hypothyroidism has been reported in a small percentage of patients [5].

Optimising the efficacy and tolerability of sunitinib

Higher exposure to sunitinib is associated with greater clinical responses [5], so maintaining optimal plasma levels of sunitinib is important. This can be achieved by administering appropriate dose levels and by minimising the risk of AE-associated treatment interruptions.

Sunitinib should be prescribed at a starting dose of 50 mg/day by Schedule 4/2, and doses can be adjusted in 12.5 mg increments [5]. Maximum plasma concentrations are reached 6-12 hours after administration and steady-state concentrations within 10-14 days [5].

Sunitinib is metabolised primarily by the cytochrome CYP450 enzyme CYP3A4. Concomitant treatment with CYP3A4 inducers (e.g. dexamethasone) or inhibitors (e.g. ketoconazole) should be avoided or doses adjusted [5]. If no alternative drug can be prescribed, the sunitinib dose should be amended to a maximum of 87.5 mg/day if co-administered with a strong CYP3A4 inducer, or to a minimum of 37.5 mg/day if given with a strong CYP3A4 inhibitor [5].

The pharmacokinetics of sunitinib are not affected by age, race, gender, body weight, creatinine clearance or performance status and no dose adjustments are necessary for mild-to-moderate hepatic impairment [5]. Sunitinib may be taken with or without food, preferably at the same time of day. If a dose is missed the patient should receive the usual prescribed dose on the following day.

Management of sunitinib-related adverse events

Pharmacists play an integral role in ensuring that required patient information is collected and patients are monitored regularly and educated about treatment outcomes, compliance and potential sunitinib-associated AEs. Pharmacists can assist in advising patients about the management of treatment-related AEs and encouraging them to report any relevant symptoms so that they derive the greatest treatment benefit. Here we review practical steps to manage AEs common to sunitinib.

Table 2: Managing adverse events observed with sunitinib therapy*

Adverse event	Pre-treatment management	Recommended strategy during treatment
Hand-foot syndrome	• Educate patients regarding HFS • Conduct full foot exam • Treat any existing conditions before treatment initiation, e.g. plantar hyperkeratosis	• Advise patients to minimise pressure on affected areas and to wear loose footwear, e.g. sandals, and to use thick socks, thick-soled shoes and shock absorbers to relieve pressure points • Recommend topical emollient creams, e.g. 99% DMSO or aloe vera, applied at least once daily or topical corticosteroids in cases of painful erythema or if symptoms; pain medicines may also be required • Podiatrist consultations, as required • Evening administration of sunitinib may reduce symptoms as maximum plasma concentrations will be reached during the night • Delay dose in patients with painful calluses (dose reductions are required rarely, usually following the first treatment cycle). Where lesions are very painful, treatment should be interrupted for 1–2 weeks
Skin toxicity, e.g. dermatitis, hair/skin discolouration	• Advise patients about possible changes in skin and hair pigmentation	• Low-dose systemic steroids, e.g. oral prednisolone, and local application of emollient creams recommended for mild-to-moderate toxicity • If severe symptoms occur, discontinue treatment and prescribe corticosteroids, then reintroduce sunitinib gradually
Oral changes, e.g. stomatitis/ulceration, pain, taste disturbance	• Educate patients on possible symptoms • Recommend switching to paediatric toothpaste and a soft toothbrush and avoidance of alcohol	• Delay or reduce dose in patients with grade 3 oral AEs • Prescribe non-alcoholic (bicarbonate) mouthwashes containing paracetamol with morphine or codeine for symptom control, Gelclair, viscous local anaesthetic gels (for lesions) and lip creams/balms (for cheilitis). Camomile, sage, arnica and zinc may also be beneficial
Hypertension	• Conduct a full cardiovascular assessment before treatment initiation • Treat unstable hypertension. If BP ≥140/80 mmHg, delay treatment • Increase dose of current anti-hypertensive therapy if appropriate	• Monitor patients regularly for BP (daily or three times per week) • Increase dose of existing antihypertensive if required and monitor in case of dose reduction/interruption of targeted therapy • Interrupt treatment or reduce dose in cases of hypertension that can not be controlled by two drugs at maximum dose or when accompanied by signs/symptoms of end organ damage or cardiovascular morbidity
LVEF decline	• Delay treatment in patients showing symptoms of CHF • If LVEF <50%, delay treatment until LVEF controlled	• Assess patients for signs and symptoms of LVEF and CHF, particularly in patients with cardiac risk factors • Interrupt/reduce dose if LVEF <50% and >20% below baseline • Dyspnoea, fatigue and oedema may suggest CHF, but can have other causes in cancer patients. Sunitinib should be discontinued in patients showing symptoms of CHF

HFS: hand-foot syndrome; DMSO: dimethyl sulphoxide; AE: adverse event; LVEF: left ventricular ejection fraction; BP: blood pressure; CHF: congestive heart failure

* Based on information from the sunitinib SPC, 2008 [5], Négrier and Ravaud, 2007 [24] and the author's opinion.

Hand-foot syndrome
HFS typically presents as painful erythema and oedema on the palms and soles, usually preceded or accompanied by paraesthesias (tingling sensations and intolerance to heat), and often associated with hyperkeratosis and desquamation. Pre-existing corns and calluses may predispose patients to symptoms on the soles of the feet.

HFS typically presents after 3-4 weeks of treatment and appears to be dose dependent, with symptoms resolving after treatment discontinuation.

Patients should be advised to relieve pressure on affected areas and apply topical creams. Patients should also be educated regarding other potential skin toxicities and their management (see Table 2) [24].

Oral changes
Oral changes including dysgeusia (taste disturbance), sensitivity and occasional sores including cheilitis (inflammation and cracking of the lips) can occur with sunitinib therapy. Symptoms typically appear within 1-2 weeks of treatment initiation but can occur variably during and between cycles and usually resolve after 1 week off treatment.

Good oral hygiene helps to reduce the incidence of oral changes. Treatment is generally palliative, including mouthwashes and anaesthetic gels (see Table 2) [24].

Cardiotoxicity
All patients should undergo a full cardiovascular examination before beginning sunitinib therapy, with regular blood pressure monitoring during treatment (see Table 2).

Hypertension can be managed easily during sunitinib treatment, through the use of appropriate antihypertensive medicines [24].

Patients with pre-existing or recent cardiovascular disease are usually excluded from sunitinib trials but may be considered for sunitinib treatment in clinical practice. These patients may be at higher risk of developing left ventricular systolic dysfunction and should undergo baseline and periodic evaluations for left ventricular ejection fraction [24].

Fatigue
Fatigue occurs commonly in cancer patients due to a variety of causes. Sunitinib-related fatigue typically occurs 2-3 weeks after treatment initiation, may worsen during weeks 3 and 4 and, in some patients, may improve during the 2-week off-treatment period.

Raising awareness of fatigue is important to manage patients' expectations so that they can make any necessary lifestyle adjustments. Patients should be evaluated for potential causes of fatigue, such as depression, hypothyroidism and anaemia, and these should be managed appropriately [24].

Hypothyroidism
Hypothyroidism can be managed effectively with levothyroxine. Patients already receiving treatment for hypothyroidism must receive regular ongoing monitoring of their thyroid hormone levels. Levothyroxine dose should be adjusted in line with any changes in hormone levels [24].

Practical measures can be adopted to minimise the impact of potential AEs.

Pharmacists can help by ensuring that regular monitoring is performed to detect any thyroid function abnormalities, enabling prompt corrective measures to be initiated.

Diarrhoea
Diarrhoea usually occurs within 2-5 days of sunitinib treatment initiation and is typically mild-to-moderate in intensity; symptoms usually improve during the off-treatment period.

Antidiarrhoeal drugs, such as loperamide, may be administered at a starting dose of 4 mg, followed by 2 mg as required up to a maximum daily dose of 16 mg. Patients should avoid spicy food, dairy products and citrus fruits [24].

Haematological abnormalities

Anaemia, neutropenia and thrombocytopenia have been observed during sunitinib treatment. Onset of non-febrile neutropenia and thrombocytopenia typically occur during Cycle 1 without subsequent progression. These changes usually resolve during off-treatment periods but may recur [24]. More progressive, cumulative neutropenia may also occur in a limited number of patients receiving prolonged treatment.

Patients with non-febrile neutropenia should maintain good personal hygiene and avoid exposure to infectious diseases. They should also avoid uncooked or unwashed vegetables and unpasteurised dairy products.

Patients with thrombocytopenia should minimise the risk of bleeding, for example by brushing teeth gently with a soft toothbrush, avoiding the use of dental floss and avoiding forceful coughing and straining with bowel movements.

Anaemia can be treated according to local treatment guidelines.

Conclusions

Sunitinib is the standard treatment for the first-line treatment of advanced RCC. Temsirolimus is recommended for patients with (modified) poor-risk mRCC and sorafenib for second-line treatment. Bevacizumab plus IFN-α2α is another option for

first-line treatment, while sunitinib represents an alternative for second-line treatment.

Sunitinib is associated with an acceptable tolerability profile. Further, practical measures can be adopted to minimise the impact of potential AEs and avoid the need for dose reductions or delays, thereby maximising patient benefit. Pharmacists can play a key role in optimising patient management by educating patients about expected treatment outcomes and AE management, and by ensuring that relevant patient data are available to clinicians.

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Non-compliance in cancer treatment

Partnership between physician and patient is always helpful, but may be vital in oncology. Non-compliance can be amazingly high, especially long term.

A common definition of compliance is the extent to which patients follow treatment instructions. Poor compliance with medical regimens is a significant problem, estimated to cost the US economy over US$100 billion (Euros 70,000 million) annually.

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The patient's active participation in the treatment is especially important during anticancer chemotherapy, which depends on high doses of toxic cytostatics and other drugs with a narrow therapeutic index. Delays in cancer diagnosis and treatment are related to a variety of factors including cultural influences, fear of cancer, financial hardship or availability and access to health care [1, 2].

In general the rate of compliance with oral drugs lies between 19% and 100% and depends on the specific clinical situation, nature of the illness and the treatment. Non-compliance with tamoxifen therapy regimens ranges between 15% and 50% when followed up at two and five years [1, 3, 4].

There are two types of non-compliance. The first one is intentional non-compliance where the patients make a specific decision not to take the prescribed medicine. It may involve a reasoned and intentioned decision by patients to omit a dose of medicine because they are asymptomatic or taking the medicine interferes with their lifestyle. The second type is non-intentional non-compliance. It is the result of forgetting or misunderstanding instructions about the drug schedule, e.g. the patient fails to obtain or to take the medicine as prescribed (in the correct dose, at the correct time), prematurely discontinues the medicine or takes the medicine inappropriately [3].

Many factors are associated with non-compliance. Knowing the main reasons for drug discontinuation may help identify those patients at risk who might benefit from special attention to compliance issues:

1. Sociodemographic factors: younger, female, fewer than 10 years of education, marital status, race, cultural influences
2. Discomfort resulting from treatment. When there is considerable efficacy, mild to moderate reactions are tolerated; however when efficacy is limited or absent, mild toxicity can lead to non-compliance. Compliance is less likely where the benefits of drugs are not obvious, e.g. a five-year hormone breast cancer regimen does not guarantee recurrence-free survival but does produce side effects
3. Preference for non-conventional forms of treatment
4. Similar pills
5. Personal judgments about the efficacy of the proposed treatment, e.g. positive-node status means complete curing
6. Unstable life mode, irregular working hours, maladaptive coping styles, e.g. denial of illness, disruptive schedules
7. Mental disorder, e.g. depression: compared with non-depressed patients, depressed patients are three times more likely to be noncompliant
8. Psychological reasons (patients with greater control over their life are more likely to comply, women who have had surgery and chemotherapy not wanting to continue hormone regimens because tablet taking is a reminder of cancer)
9. Insufficient explanation of therapeutic decisions, disturbance in the doctor-patient communication, too many doctors treating the patient.

Today the increase in patient autonomy has led to the terms 'concordance' and 'adherence' replacing the more authoritarian term 'compliance'. The most common definition of adherence is 'the extent to which a person's behaviour coincides with medical or health advice' [3, 4]. The UK Medicines Partnership defines drug concordance as "an agreement reached after negotiation between a patient and a healthcare professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines are to be taken" [5].

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Nuclear medicine needs radiopharmacists!

Having a radiopharmacist as part of the team at a large teaching hospital brings added value. After all, the radiological requirements of a product are additional to the usual pharmaceutical requirements. Research success is also possible when experts in several fields work together.

Introduction

A radiopharmaceutical is a medicinal product that contains a radionuclide. Radioactive materials are often associated with the treatment of cancer. However, the vast majority (~80%) are used in diagnostic techniques for a wide range of diseases (see Figure 1). Of these, the majority are used in imaging techniques. In comparison, a small but very important number are used for therapy.

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Radionuclides used in medicine have limited physical lives meaning that their radioactivity declines relatively quickly. Radiopharmaceuticals usually consist of two parts: a tissue-specific molecule and a radionuclide. After injection into the patient, the tissue-specific part concentrates the radiopharmaceutical in the tissue under investigation, where the radiation emitted by the radionuclide is used for imaging in a diagnostic study or to destroy harmful cells in radiotherapy. In conventional imaging with radiopharmaceuticals that contain gamma-emitting radionuclides, the photons emitted are detected by an instrument known as a Gamma camera and an image of the organ is constructed (see Figure 2). More recently, positron emission tomography (PET) has entered the market with detection of photons emitted by the annihilation reaction between a positron and an electron in the body. This instrumentation affords better resolution, higher sensitivity and uses radiopharmaceuticals that consist of radiolabelled molecules that are very similar in chemical structure to endogenous substances or drugs [1].

The limited physical half-life means that the radiopharmaceutical must usually be formulated close to the patient in hospital. Radiopharmacists have a crucial role in radiopharmaceutical production but their roles in the nuclear medicine department are numerous. The pharmacist is close to both production and quality assessment but also to the patients undergoing examination. The profile of tasks is of interest to the discipline of hospital pharmacy and of great importance for a quality clinical nuclear medicine department that wishes to achieve high quality examinations.

Safety and efficacy

The principal role of the pharmacist in nuclear medicine is no different to other branches of medicine - to ensure safety and efficacy. Safety of the patient includes for example ensuring that the product is sterile, free from particles and has the correct activity.

Safety of the members of staff working in the radiopharmacy is also an important responsibility. Efficacy means that the radiopharmaceutical behaves as expected when it is administered to the patient.

The radiopharmacy sequence

Radiopharmacy procurement

In several countries the ordering of radiopharmaceuticals is the responsibility of the local hospital pharmacy. The radiopharmacist may also have the task of ensuring compliance with the regulations relating to the receipt, storage and disposal of radioactive materials and is responsible for the quality of the starting materials.

Receipt of order/prescription

The nuclear medicine physician must be authorised to prescribe radiopharmaceuticals. As with professional checking of any prescription, there is the need to confirm that the prescribed radioactivity dose is appropriate for the indication and that the radiation dose is within limits to afford a valuable investigation without harming the patient.

Preparation

The radiopharmacist is responsible for radiopharmaceutical production or has a release function for products prepared in the radiopharmacy. He is also responsible for ensuring that the products are manufactured according to Good Manufacturing Practice (GMP) with respect to documented and validated methods with adequate quality control and undertaken in facilities for aseptic production by personnel educated and certified for radiopharmacy work.

Safe procedures

Working techniques must be monitored not only with respect to aseptic preparation but also radiation safety. Usual methods to ensure radiation safety are radiation shielding, handling techniques, monitoring for contamination with radioactivity and the dose received by members of staff.

Radiopharmaceuticals are produced in special units for aseptic production similar to those for cytotoxic drug preparation. Adequate protective clothing, proper working techniques and a monitored environment are essential for good quality. Regular testing is required as for any other pharmaceutical production of sterile medicines.

Quality control

There is a limited time available for quality control (QC) tests before the product is delivered to the patient examination area. All procedures must be thought through carefully. The whole

Figure 1: ^{99m}Tc-Succimer image of the kidneys showing diseased left kidney

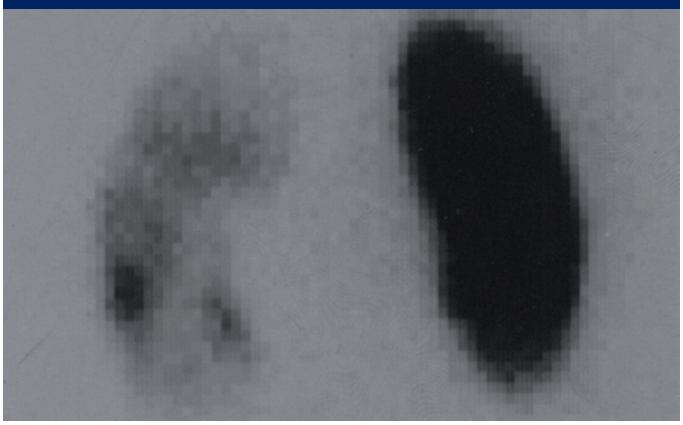
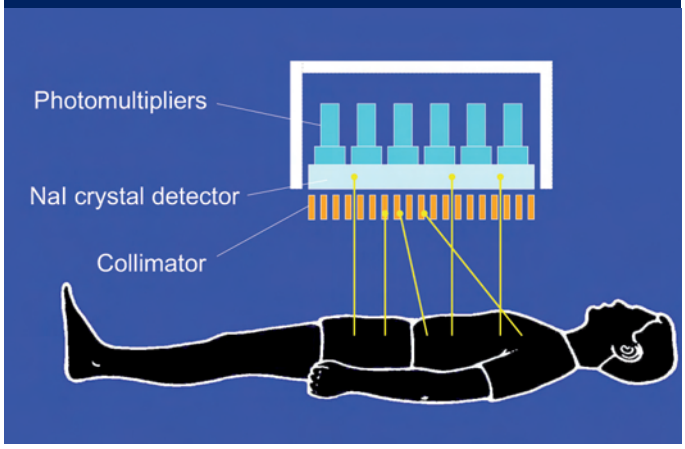


Figure 2: The operation of a Gamma camera



batch is often one vial! The radiopharmacist has to check the radionuclide identity and purity, do all the normal QC checks as well as a radioactivity and endotoxin check within a very short time frame and with minimal exposure of the staff to radiation.

Quality assurance

The education of the pharmacist provides an expert basis for quality assessment and management. Expertise in GMP and other regulations governing aseptic small scale extemporaneous production is essential to ensure that products meet the required standards.

Quality assurance is the only task for many hospital pharmacists in the nuclear medicine department. This is not enough. Only by experiencing the daily routine of radiopharmaceutical preparation and assessment of quality can the radiopharmacist gain the expertise to adequately handle problems and questions that arise.

Transport

The specialised nature of radiopharmacy means that products are often prepared in a central radiopharmacy and transported to nuclear medicine departments in other hospitals. The radiopharmacist is responsible for ensuring that transport of radioactive materials by road complies with the complex set of regulations.

Injection into the patient

The radiopharmacist must also work as a clinical pharmacist in the wards and clinics. Drugs taken by the patient are known to affect the biodistribution of certain radiopharmaceuticals. The pharmacist may advise on interactions and suggest better dosing schemes or drugs. Advice on thyroid blocking can also be requested when a radiopharmaceutical containing a radioisotope of iodine is being administered.

Reporting

The radiopharmacist also plays a part in the final image and quality assessment. Advice may be requested to explain an unusual biodistribution of the radiopharmaceutical that affects the reporting of the investigation. The further reporting of the unusual biodistribution is also important and there is a European scheme for this. Mistakes in radiopharmaceutical production are rare but must be considered carefully.

Although adverse reactions to radiopharmaceuticals are relatively rare, their reporting is valuable and again, there is a European scheme for this.

Research and development of radiopharmaceuticals

In addition to the routine preparation of radiopharmaceuticals, radiopharmacists have made important contributions to research and development. The projects arise mainly from two sources:

- Products manufactured in the hospital radiopharmacy
- Products prepared for use in research

This is perhaps the part of the job from which the radiopharmacist derives the greatest satisfaction, and can be illustrated by the following example.

A breast surgery department requested ^{99m}Tc albumin nanocolloid for intraoperative localisation of sentinel nodes. As the members of staff in this department 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 in the radiopharmacy to validate a syringe as a suitable container: adsorption of the radiocolloid to the syringe, labelling efficiency by thin-layer chromatography and particle size by Nuclepore filtration and photon correlation spectroscopy. This radiopharmaceutical is now supplied routinely in syringes [2].

Another example that required scientific investigation arose from the identification of a poor quality product. Routine measurements of the radiochemical purity of the renal imaging agent ^{99m}Tc-MAG3 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 MAG3 kits. Elimination of the problem was achieved by using two-piece syringes [2]. Occasional low radiochemical purity has also been observed when MAG3

kits are reconstituted with sodium chloride injection from plastic ampoules. Investigation of this phenomenon revealed that this occurred with plastic ampoules that had been exposed to light. The problem was overcome if either plastic ampoules are protected from light or sodium chloride injection from glass containers is used [3].

An example of radiopharmaceutical development is ^{177}Lutetium-radiolabelled octreotate which is now used in many nuclear medicine centres (see pages 16-17), for treatment of endocrine tumours.

PET is still a very powerful research tool and PhD projects conducted by pharmacists are common in many centres around the world.

Conclusion

Expertise and inter-profession collaboration are essential for added value in radiopharmaceuticals preparation, handling and examination. PET technology is a new field of calling. The fascinating work of a radiopharmacy department such as might be found at a university hospital where research is conducted is a challenge for radiopharmacy but also for young colleagues interested in clinical pharmacy. Routine production of radiopharmaceuticals is largely automated for reasons of safety and speed. Therefore, the pharmacist's expertise may be called upon firstly to help design the building in which the cyclotron is sited and the products prepared; to design the production process and quality control procedures to meet all the applicable regulations, and to collaborate with physicians. The latter usually means devising a suitable radiopharmaceutical for a particular diagnostic test or research projects. Such multidisciplinary work is vital for the success of the nuclear technique, and requires pharmacists who are experts in this field. Nuclear medicine is calling for radiopharmacists!

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Radiotherapy of neuroendocrine gastro-enteropancreatic tumours: new principles

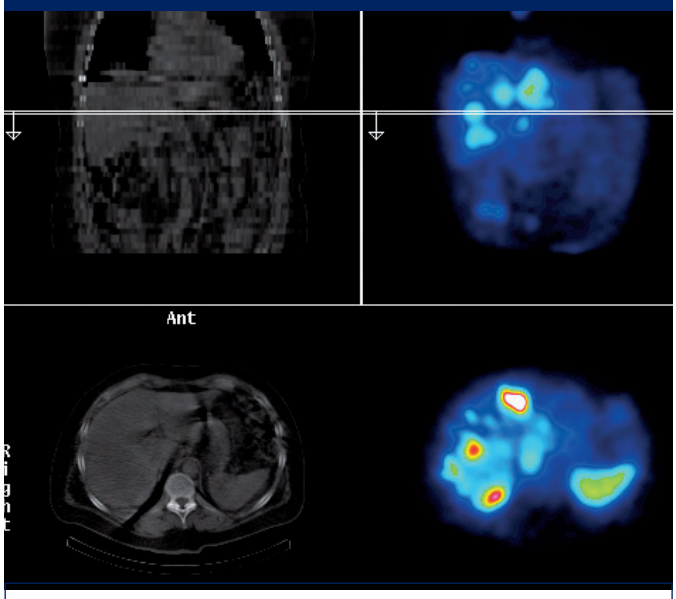
Somatostatin analogue vectors carry radioactive chemicals to their target, improving the treatment of neuroendocrine gastro-enteropancreatic tumours.

Aseel Cherif

Neuroendocrine gastro-enteropancreatic tumours constitute a heterogeneous group of tumours that originate from the neuroendocrine system in the gastrointestinal tract. Gastrinomas, insulinomas, carcinoids, glucagonomas, somatostatinomas and some other non-classified tumours are among the tumours classified as neuroendocrine. The tumours are often difficult to diagnose and cause high morbidity and mortality with a five-year survival of 50% [1, 2]. Today surgical resection offers the only possibility of curing patients with neuroendocrine tumours. Unfortunately, not all tumours are available for surgery and moreover these tumours have a tendency to form metastases and produce hormones. Other treatment alternatives such as cytotoxic drugs, immunomodulators, e.g. interferon; and radiation therapy have been tried but have shown limited success on disease progression and survival.

Human somatostatin is a 14-amino-acid cyclic peptide with a single disulfide bridge. It belongs to a family of peptides with variable molecular weights. The larger forms are classified as hormones. The elimination half-life of the natural hormone somatostatin is only a few minutes, making it of no value in routine therapy. Octreotide has a half-life of several hours, making intermittent therapy possible. Somatostatin analogues such as octreotide and lanreotide have been used clinically to treat gastro-enteropancreatic tumours since the

Figure 1: ^{177}Lutetium being delivered to the site of the tumour



Uptake of ^{177}Lutetium-octreotate in neuroendocrine tumours seen in parallel with computerised tomography (CT)

early 1980s. The analogues are synthetic somatostatin-octapeptide derivatives with structure and activity similar to the somatostatin hormone and have both cytostatic and cytotoxic effects on the tumour cells. The drugs give symptom relief, increase survival time, but give no cure [3].

In recent years there has been increased interest in tumour-directed radiotherapy using somatostatin analogues as radioactivity vectors. A number of preparations such as ^{111}Indium DTPA-octreotide, ^{90}Yttrium DOTA-octreotide and later ^{177}Lutetium DOTA-octreotate have been developed with promising clinical results [4, 5]. DTPA and DOTA are ligands designed to bind radioactive chemicals to somatostatin analogues. Studies have reported a 50% clinical and biochemical improvement in patients with neuroendocrine gastro-enteropancreatic tumours. The somatostatin analogue, coupled to optimal radioactivity, has limited uptake in surrounding tissues such as the bone marrow and kidneys and maximum uptake in the tumour.

(^{177}Lutetium-DOTA(O)Tyr3) octreotate, developed in The Netherlands, is an improvement and is used by several sites in Europe. ^{177}Lutetium has a physical half-life of 6.7 days and decays by beta particle emission with a mean energy of 0.149 MeV and gamma emission with a mean energy of 0.208 and 113 MeV. The range of ^{177}Lutetium is eight millimetres in air and two millimetres in water. This is important for the treatment of small tumours.

Experimental and clinical studies have shown that the somatostatin analogue Tyr3 chelated with DOTA has a significantly higher affinity for somatostatin receptors than the Tyr3-octreotide. Compared with ^{111}Indium-octreotide a three to four times higher uptake can be obtained using ^{177}Lutetium-octreotate but with a similar biodistribution in other tissues such as the liver, spleen and kidneys. The elimination of ^{177}Lutetium-octreotate is faster than that of the ^{111}Indium-octreotide analogue and gives a significantly lower 24 hour urinary excretion fraction. Further advantages of ^{177}Lutetium-octreotate to ^{111}Indium-octreotide are significantly more efficient tumour inhibition in animal models, allowing the dose to be measured accurately and making studies with positron emission tomography possible using the same radionuclide [6]. The tissue penetration of ^{177}Lutetium is better than that for ^{90}Yttrium particularly for smaller tumours where a large proportion of the ionisation radiation from ^{90}Yttrium is lost in surrounding tissue (see Figure 1).

Because of these advantages, ^{177}Lutetium-octreotate is therefore a promising new alternative in the treatment of neuro-endocrine tumours.

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Joint venture in continuing education

Geoff Saunders
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The United Kingdom is seeking to establish standards and accreditation in the competency of oncology pharmacists, in moves that run parallel to those of ESOP (see pages 4-6).The Faculty of Cancer Pharmacy has been formed to improve patient care by providing the opportunity for pharmacists and technicians in the field of cancer care to undertake accredited training and assessment, leading to formal recognition of their knowledge and skills. This body is a joint venture between the British Oncology Pharmacy Association (BOPA) and the College of Pharmacy Practice, an independent professional association for pharmacists [1]. It was formally launched in January 2008 at the Hospital Pharmacy Conference. The six members of the faculty board were chosen by the BOPA membership and held their first meeting in April.

Assessment process

A number of standards within practice, or frameworks, have already been developed by the Competency Development and Evaluation Group of the college and have received national recognition [2]. The frameworks have been validated through practice research. The faculty board has decided to adopt these competency standards, known as the General Level Framework and the Advanced and Consultant Level Framework (ACLF) to support the assessment of aspiring members. The General Level Framework has been shown to improve the practice of newly qualified pharmacists [3] and the ACLF to describe different levels of practice consistently across various pharmacy specialities [4]. These competency frameworks describe competencies for pharmacists across a number of domains encompassing clinical knowledge, managerial and leadership functions as well as educational and research roles. Specific cancer-related pharmacy competencies at Foundation, Excellence and Mastery levels previously published by BOPA [5] add to these frameworks by providing oncology-specific clinically oriented competencies for pharmacists to focus on.

How accreditation is gained

Prospective candidates self assess their practice against the frameworks and submit a portfolio of evidence to substantiate their perceived level of practice. This is examined by two acknowledged cancer pharmacy experts appointed by the faculty who together with a third assessor appointed by the college from a different speciality, with experience of assessment, will interview the candidate to clarify any issues raised by examining the portfolio and to agree the level of membership conferred.

Accreditation is offered as membership of the College of Pharmacy Practice. There are three levels: Practitioner Member, assessed using either the general level framework or the foundation elements of the ACLF; Advanced Membership and Fellowship of the College are assessed using a defined combination of Excellence and Mastery clusters of the ACLF

Accreditation of educational materials and events

The Faculty also aims to support the professional development of pharmacists within the field of cancer pharmacy by providing accreditation of both educational materials and events. To do this it is drawing together existing materials from the College of Pharmacy Practice, BOPA, the Pharmaceutical Society of Great Britain and the Department of Health's Knowledge and Skills Framework.

Conclusion

BOPA and the Faculty of Cancer Pharmacy firmly believe that a robust and aspirational accreditation system is the correct path forward for pharmacists specialising in the area of oncology. We believe the process will be credible to our own profession, and to the multidisciplinary team. We think the benefits of such a process are:

- Recognition that comes with membership of a prestigious speciality body
- Additional recognition for high-level achievement, e.g. fellowship or merit awards
- A focus for developing and delivering professional views plus input into national initiatives and policy development
- A professional network for peer support, peer review and peer pressure, linking into clinical governance agenda
- Accredited commissioning and/or delivery of education and training targeted at specialist needs
- Improving patient care.

To date one fifth of UK oncology pharmacy staff who are members of BOPA have shown a commitment to specific oncology pharmacy accreditation by joining the Faculty of Cancer Pharmacy as associate members with the expectation that they will proceed to full membership through the assessment process previously described. An opportunity has arisen to work with oncology pharmacists practising in Australia. With the emigration of one of the founding members of the faculty it is hoped that existing links with cancer pharmacists in Queensland can be used to replicate the UK initiative.

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Comment

Europa Uomo in collaboration with ESOP

Europa Uomo is a confederation of patient support groups in 21 European countries. We inform and educate our members with the support of professional bodies. Closer collaboration with the ESOP is overdue and joint projects will be started in the near future.

Europa Uomo was officially established with the support of the European School of Oncology (ESO) and the Oncology Center Antwerp (OCA) in 2004 [1, 2]. The need for a European patient support group, following the example of our sister organisation Europa Donna, became clear in view of the ever-increasing diagnosis of prostate cancer in European men. Indeed the cancer statistics show that cancer affects one in three European citizens and kills one in four people. More to the point, breast, colon, lung and prostate cancers are the most common forms of cancer as they account for more than half of the entire cancer population in the European Union. Prostate cancer is by far the most frequently diagnosed form of cancer in men (24.1% of all cases and 10.4% of cancer deaths). The difference adds up to the prevalence and we estimate that more than three million prostate cancer survivors live in Europe [3].

Professor Louis Denis

Europa Uomo, the European Prostate Cancer Coalition, represents and supports national patient groups focused on prostate diseases in general and prostate cancer in particular. Our aims are simple. First, to develop individualised prostate cancer treatment based on the best medical treatment as recognised in official guidelines and good clinical practice. This treatment results from experts working closely as a multi-professional group and provides patient advocates and support groups with a biannual update on medical sciences and practice of their peers. We have a scientific committee of European experts to provide this constructive service. The other side of the coin is evidence-based, holistic patient care where each and every one of us should be involved as a partner with the professionals. In the period 2008-2009 we are basing our awareness on the key points provided by the European Association of Urology and presented below.

Defined Key Topics 2008-2009

Prostate conditions

- Most men will develop benign prostate disease and many of them will develop complaints for which both medical and surgical treatments are available and are highly effective.
- Prostate cancer can only be cured when it is detected in its early stages, i.e. when the disease is organ-confined; these treatments are often curative. PSA and PSA kinetics - PSA velocity or PSA doubling time - are helpful tools to recognise patients at risk of having prostate cancer.
- Cancers diagnosed by early detection programmes do not always need treatment. Active monitoring for selected patients is a reasonable option that still allows to initiate curative treatment during follow-up when needed.
- Hormonal therapy affects the quality of life severely but when it is needed, the side effects can be reduced by instruction about nutrition, physical activity and psychological support.
- A family history of prostate cancer may be significant; please check your sons and brothers.

Incontinence

Bladder symptoms are common in men in the age group when prostate disease occurs. They may be related to overactivity of the bladder rather than to prostate disease and are amenable to treatment. This should be checked since specific treatment is indicated.

Erectile dysfunction (ED)

- ED may be the presenting symptom of hypertension, hyperlipidaemia, diabetes and hormonal changes. It is important that all men with ED are assessed for the presence of such conditions.
- The urologist is the specialist who can best advise on the prevention and control of both lower urinary tract symptoms and ED, which are commonly associated with each other.

Our rapid expansion is not only based on committed, free, professional support, the recognition of the cancer patients' rights by the European Commission and Parliament but also by our internal basic discipline as expressed in our Manifesto (see below). It took more than a year to agree on the text, and quality of life did not arrive at the number one point by accident. You cannot be a member if you don't subscribe to these 10 basic rules.

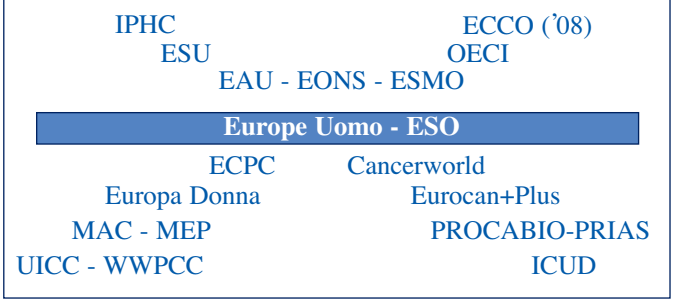
Europa Uomo Manifesto

1. To find ways and means of promoting quality of life for prostate cancer patients and their families
2. To promote the dissemination and exchange of evidence-based, factual and up-to-date information on prostate cancer
3. To promote prostate awareness and the adoption of appropriate diagnoses and prognoses
4. To emphasise the need for appropriate early detection
5. To campaign for provision of and access to the best treatment
6. To ensure quality, supportive care throughout and after treatment
7. To promote multi-professional quality care and appropriate medical infrastructure
8. To acknowledge good clinical practice and promote its development
9. To ensure that all men fully understand any proposed treatment options, including entry into clinical trials and their right to a second opinion
10. To promote the advance of prostate cancer research.

It is also clear that the last point is no accident as we solidly support scientific research. We are painfully aware that the lack of a reliable marker for the future aggressivity of any tumour leaves all of us in limbo. Fortunately we see progress after each and every cancer meeting but a broad, in-depth reappraisal of the therapeutic and pharmacological options is needed. Just think of the time and money it takes for an hypothetical drug to reach the bedside of the patient. Fellow survivors cannot afford a waste of time and look for an appropriate reduction in time and expense between the laboratory and the bedside. We are active partners in the Transmark project of Professor C Bangma in the call FP7-PEOPLE-ITN-2008.

We have a number of active partnerships as shown in Figure 1 but we look forward to adding ESOP to this list.

Figure 1: Europa Uomo partnerships



We believe that such a partnership could help us raise the priority for off-label use of cancer drugs, cross-border treatment, complementary and alternative medicinal products and the support of hospital and community pharmacists in preventing the dissemination of misleading information and the prevention of avoidable side effects and drug interactions.

We come closer to the industry by discussing risk sharing and patients' responsibilities in clinical trials.

We meet in a few weeks in Hamburg, Germany, and we hope that our German member Bundesverband Prostatakrebs Selbsthilfe will take on a pilot programme as a joint project.

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Erratum

The EJOP apologises for having printed the wrong captions for Table 1 in the article "Tumour lysis syndrome – prevention and treatment" by Mr Michael Hoeckel in EJOP 2008;2(2):22.

The correct captions for the table are shown below.

Table 1: Onset of clinical features of TLS

Clinical problem	Chemotherapy	Hyperkalaemia	Hyperphosphataemia, hypocalcaemia	Hyperuricaemia	Acute renal failure
Time (days)	0	0.25 - 3	1 - 2	2 - 3	3 - 4

Business as usual and some surprises

More than 25,000 experts attended the 50th American Society of Hematology (ASH) Annual Meeting in San Francisco, USA in December 2008. Advances were discussed in the treatment of several diseases and the improved and simplified treatment of others.

The diseases for which treatment has advanced were leukaemias and lymphomas, thromboembolic disorders, severe infections, autoimmune diseases and genetic aberrations in haematological diseases. Impressive results were presented regarding more effective and less complex strategies in anticoagulation, platelet transfusion and the treatment of chronic lymphocytic leukaemia (CLL).

Professor Günther J Wiedemann, MD, PhD

Professor Wolfgang Wagner, MD, PhD

Leukaemias and lymphomas: improvements in difficult-to-treat forms

Ongoing research is focussing on new, investigational treatments as well as on new combinations of treatment options that have been used for years.

Czuczman and co-authors presented an international phase II study confirming the efficacy of lenalidomide for patients with relapsed, aggressive lymphoma. The trial included 73 patients with refractory or relapsed diffuse large B cell lymphoma (DLBCL), the most common form of non-Hodgkin's lymphomas. All patients had received at least one prior treatment. In spite of failure of aggressive treatment such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab or high-dose chemotherapy and stem cell transplant, the overall response rate to lenalidomide was 29% (25% partial, 4% complete response). Stable disease was achieved in 15% of patients. The authors interpret these results as a possible future treatment option for highly-refractory patients suffering from this type of non-Hodgkin's lymphoma.

Czuczman M et al. Confirmation of the efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory diffuse large B cell lymphoma (Abstract #268)

Hallek and co-workers found that in untreated patients with advanced chronic lymphocytic leukaemia (CLL) combination therapy with fludarabine, cyclophosphamide and rituximab (FCR) was significantly more effective than treatment with fludarabine and cyclophosphamide (FC) alone. After two years of follow-up the overall response rate was 95% in the FCR arm as compared to 88% in the FC arm. Complete responses were seen in 52% in the FCR group (27% in the FC group). Progression-free survival rates were 76.6% and 62.3%, respectively. The authors conclude that FCR has the potential to become the new first-line standard treatment in advanced CLL.

Hallek M et al. Immunochemotherapy with fludarabine, cyclophosphamide and rituximab vs. fludarabine and cyclophosphamide improves response rates and progression-free survival of previously untreated patients with advanced chronic lymphocytic leukaemia (Abstract #325)

Schrappe and co-authors presented a study on 3,655 children (ages 1-17 years) suffering from acute lymphoblastic leukaemia (ALL). They were randomised to receive either dexamethasone (10 mg/m^2/d) or (the standard) prednisone (60 mg/m^2/d) as part of the induction therapy in addition to vincristine, daunorubicin and L-asparaginase. After six years of follow-up patients who received dexamethasone showed event-free survival in 84.1% as compared to 79.1% in the prednisone group. The six-year cumulative incidence of relapse was 11% (dexamethasone) and 18% (prednisone). Dexamethasone treatment, however, led to higher toxicity mainly in terms of severe infections.

Schrappe M et al. Dexamethasone in induction can eliminate one-third of all relapses in childhood acute lymphoblastic leukaemia (Abstract #7)

Transfusion medicine: new strategies in management of thrombocytopenic patients

Several studies with the potential to change clinical practice presented evidence-based data to determine the optimal use of platelets or medications to be given to severely thrombocytopenic patients.

In a large multi-centre phase III trial, Zaja and co-authors could show a significantly better sustained response (platelet counts >50 x 10^9/L from one to six months) in patients with ITP (idiopathic thrombocytopenic purpura) when dexamethasone was combined with rituximab compared to dexamethasone alone. In patients treated per protocol, a sustained response was achieved in 85% with dexamethasone/rituximab (39% with dexamethasone alone).

Zaja F et al. A prospective randomized study comparing rituximab and dexamethasone vs. dexamethasone alone in ITP (Abstract #1)

Slichter and co-workers proved in a large-scale clinical trial that low-dose transfusion of platelets (1.1 x 10^{11} plt/m^2) is as effective as medium- and high-dose platelets (4.4 x 10^{11}

plt/m^2) in preventing bleeding and the need for red blood cell transfusions in hypoproliferative thrombocytopenia due to chemotherapy or stem cell transplant. These results will help to reduce costs and prevent shortages in blood supply.

Slichter SJ et al. Effects of prophylactic platelet dose on transfusion outcomes (Abstract #285)

Wandt and co-authors found that patients who had undergone high-dose chemotherapy and stem cell transplantation were not harmed when they received platelet transfusions only in the case of relevant bleeding (high-risk patients with e.g. sepsis or systemic aspergillosis were excluded). Compared to the control group (traditional prophylactic treatment with platelet transfusion if platelet count was <10/nL), patients in the study group received significantly fewer platelet transfusions, resulting in a total reduction by 27% in the study group. These patients experienced, though, more minor bleedings but no life-threatening or fatal bleeding. The authors conclude that one quarter to one third of all platelet transfusions are given unnecessarily.

Wandt H et al. A therapeutic platelet transfusion strategy without routine prophylactic transfusion is feasible and safe and reduces platelet transfusion numbers significantly (Abstract #286)

Cheng and co-authors showed that long-term eltrombopag therapy (versus placebo) increased platelet counts, decreased bleeding and the use of rescue medications and allowed for a reduction of baseline therapy in patients with chronic idiopathic thrombocytopenic purpura (ITP). Patients in the treatment group were eight times more likely to achieve platelet counts between 50/nL and 400/nL during the six months of treatment. Platelet counts never exceeded 30/nL in the placebo group, while median platelet counts rose from 52/nL to 91/nL in the eltrombopag group. Significantly fewer patients treated with eltrombopag experienced any bleeding. The substance seems to be an important new treatment option.

Cheng G et al. Oral eltrombopag for the long-term treatment of patients with chronic idiopathic thrombocytopenic purpura (ITP) (Abstract #400)

Thrombosis: Advances that improve anticoagulation

Venous thromboembolism is a serious public health problem. Cancer patients are at elevated risk. A large-scale study showed that cancer patients, especially with lung and pancreatic cancer, could benefit from the preventive use of anticoagulants. A new class of anticoagulants (factor Xa inhibitors) is currently being investigated in promising phase III trials.

Buller and co-authors examined the efficacy of the new factor Xa inhibitor idrabiotaparinux as compared with idraparinux. Idrabiotaparinux links idraparinux to biotin, thus allowing its effect to be antagonised if necessary by infusion of avidin, an egg protein that binds with biotin. Both substances were equally effective in preventing deep-vein thrombosis with a trend towards less bleeding with idrabiotaparinux (clinically relevant bleeding 5.2% vs. 7.3%, major bleeding 0.8% vs. 3.8%) By an infusion of avidin, mean anti-factor Xa activity could be reduced by 77.8% within 30 minutes and was sustained for at least five days.

Buller HR et al. Idrabiotaparinux, a biotinylated long-acting anticoagulant, in the treatment of deep venous thrombosis (EQUINOX Study): safety, efficacy and reversibility by avidin (Abstract #32)

Agnelli and co-workers evaluated the efficacy of nadroparin, a low-molecular-weight heparin, for the prevention of thromboembolic events in cancer patients receiving chemotherapy. Almost 1,200 patients were randomised to receive nadroparin (3,000 IU once daily SC, maintained for the duration of chemotherapy or up to a maximum of four months) or placebo. Thromboembolic events occurred in 2.1% of the nadroparin group vs. 3.9% of the placebo group ($p = 0.033$), 0.7% in the nadroparin group experienced a major bleeding.

Agnelli G et al. A randomized double-blind placebo-controlled study on nadroparin for prophylaxis of thromboembolic events in cancer patients receiving chemotherapy (Abstract #6)

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11th Annual Symposium of the British Oncology Pharmacy Association

Methods for minimising chemotherapy-induced toxicity provided a key topic at the 2008 symposium for British oncology pharmacists.

Around 700 delegates and speakers convened in Liverpool, in north-west England, for the 11th Annual Symposium of the British Oncology Pharmacy Association (BOPA), held 17–19 October 2008. The programme, which featured more than 40 presentations and workshops across four themes (Hot Topics, Cancer 2012, Clinical Update, and Introduction to Oncology) attracted oncology pharmacists and other cancer specialists from as far afield as Greece and the US, as well as the UK. Klaus Meier spoke on European collaboration on behalf of ESOP, which was well represented.

Janis Smy
BSc

Prevention and management of serious side effects

Dr Zafir Malik, a consultant clinical oncologist from Merseyside and Cheshire Cancer Network, presented a range of evidence demonstrating the efficacy of granulocyte-colony stimulating factors (G-CSF) when used to prevent potentially life-threatening chemotherapy-induced neutropenic sepsis (NS). He pointed out that European and US guidelines recommend primary prophylaxis with G-CSF for patients receiving regimens associated with an NS risk of over 20%, or at lower levels in the presence of other known risk factors. Citing patients with early-stage breast cancer as an example, he said that neutropenia led to dose delays in 58% of chemotherapy recipients, and to dose reductions in 53%, yet there was evidence that reduced dose intensity resulting from such treatment modifications was associated with reduced survival in this patient group. Should a patient develop NS, he recommended a step-down treatment approach, based on empirical parenteral antibiotics on admission to hospital, to be continued or switched to oral antibiotics, depending on the patient's condition and temperature.

The importance of well planned, effective out-of-hours care pathways for admission and treatment of chemotherapy-induced toxicities were emphasised by Dr David Jackson, a consultant medical oncologist from St James's University Hospital, Leeds. He pointed out that NS, mucositis, diarrhoea, nausea and vomiting and cytotoxic extravasation were all potentially life-threatening and warranted urgent therapy. However, as his series of case reports illustrated, essential investigations and interventions were often delayed or omitted because of lack of information in the receiving ward and poor communication within and between hospitals. He called for the development of robust patient care pathways, built around effective communication and information channels.

Safety of intrathecal therapy

Denise Blake, a pharmacist from Newcastle Royal Infirmary, delivered a plea for safe use of intrathecal chemotherapy, the subject of recently updated national guidelines from the UK Department of Health*. She reminded delegates of some of the tragedies intrathecal chemotherapy in the UK and other countries, and urged pharmacists to read the latest information thoroughly. Key changes in the 2008 update include a requirement for healthcare professionals involved in administering an intrathecal treatment to make sure all personnel are appropriately trained and registered. In addition, use of mini-bags is now recommended for the delivery of vinca alkaloids, except in a paediatric setting.

Role of vascular endothelial growth factor inhibition

Angiogenesis inhibition in cancer treatment was one of the Hot Topics of this year's symposium. Andrew Clamp, a senior lecturer in medical oncology at Christie Hospital, Manchester, UK, outlined how angiogenesis was controlled in normal tissues, but uncoordinated in cancer, and explained the role of vascular endothelial growth factors (VEGF) in the proliferation of blood vessels. He said that VEGF inhibition was associated with serious side effects and emerging drug resistance. However, treatment efficacy and tolerability could be improved through use of drug combinations and sequencing and dose modification. Moreover, there were encouraging results from studies of biomarkers that predict patients likely to benefit from anti-angiogenic therapy, or detect the early signs of progressive disease. Such markers could be used to optimise treatment efficacy, minimise toxicity and reduce the costs associated with ineffective or poorly tolerated treatments.

The 2009 BOPA Annual Symposium will be in Brighton, Sussex, 16-18 October (see www.bopawebsite.org).

*www.dh.gov.uk/en/index.htm search for HSC 2008/001

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