On behalf of the ECOP 2012 Conference Committees, we would like to acknowledge the collaboration and support of our official media partner:

- EJOP - European Journal of Oncology Pharmacy

EJOP • Volume 6 • 2012 • Issue 3-4 • €50

EJOP
European Journal of Oncology Pharmacy

www.ejop.eu

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

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ISSN EJOP: 1783-3914

Print Run: 3,000 Printed by PPS sa

PPM Pharma Publishing Media EUROPE
Published in Belgium by Pharma Publishing & Media Europe
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Individual:	€170	€200
Hosp/Uni:	€330	€360
Instit/Corp:	€420	€450
Student:	€130	€160

Individual and student subscriptions are subject to 21% VAT Belgian Government tax.

The water usually runs down the hill, but the spirit is able to climb!

As we present this issue of *European Journal of Oncology Pharmacy* (EJOP), the first European Conference of Oncology Pharmacy has already taken place in Budapest, Hungary, 27–29 September 2012. Over 500 delegates from nearly 50 countries attended the conference, and it was a great opportunity to forge connections between delegates. Europe seems to be as great in mind as it is in reality.

Klaus Meier
Editor-in-Chief

The European approach to friendships and collaborations is well known, and this was witnessed in the talks and presentations given at the conference. What emerged was a real sense of worldwide partnership between oncology pharmacists.

Many local delegates had the opportunity to participate. The scientific programme, which included clinical and practice streams, attracted more delegates than expected, and enabled best practice and experiences to be disseminated and shared.

In the next few issues of EJOP, we will give those who were unable to attend an opportunity to learn more about the outcome of the discussions and presentations. In the meantime, all members are able to read the abstracts online (www.ppme.eu), and are encouraged to establish contact with speakers who presented topics of personal interest.

The desire to integrate new ideas into daily practice is tempered by other unforeseen demands. The cancer drug shortage, for example, is continuing. Difficulties are occurring in other areas, for example, changes to package size and lack of availability of certain antibiotics and the need to find substitutes. For oncology, the issue is mutating into a problem.

In the US, the Community Oncology Alliance reported that nearly 98.9% of 525 clinicians surveyed experienced a shortage of a cancer drug in the previous year [1].

Availability of many different oncology drugs has been restricted. Thirty years ago, Germany was coined the 'pharmacy of the world'; however, the shortage of only one drug, fluorouracil, used in nearly 30% of all treatments, brought the treatment of these patients to a near standstill. The deliveries proceeded some weeks later. The German Society for Oncology Pharmacy (DGOP) has since begun to collate data on this incident from all 700 pharmacies preparing cytotoxic drugs. These data are sent to the Ministry of Health in Berlin, Germany, each week to inform decision-making.

Shortage of drugs has also prompted EMA to take action. On 22 November 2012, the agency published a 'reflection paper on medical product supply shortage caused by manufacturing practice compliance problems' (EMA/590745/2012) [2]. A safety report of 23 September 2012 from the Institute for Safe Medication Practices was cited. It showed evidence that a disruption in the supply of medicines can lead to *inter alia*, a failure to treat. The report also highlighted that less desirable, often expensive, unfamiliar alternative medicinal products are being used, and that the potential for error and poorer patient outcomes has increased as a result of absent or delayed treatment. The increased incidence of preventable adverse events associated with alternative medicinal products or dosage forms was also underlined.

We cannot say that shortage of drugs will only occur in countries that are unable to pay the highest price. It is, in fact, monopolisation that drives companies to merge and consolidate production plants for one drug. This situation is incompatible with our goals of providing the best care for people with cancer.

Instead of improving our service based on increasing knowledge, the economic situation drives us to be only hunter after the daily needed drugs.

ESOP has to make its voice heard: its message to politicians should be that health is a basic human necessity, and it is a political responsibility to ensure that healthcare provision, particularly for people with cancer, should be affordable and accessible.

In view of these circumstances, I hope that this issue of EJOP will help increase knowledge of how pharmacists can play a role in improving health care.

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ECOP 2012 Conference Report

ESOP held its first conference from 27–29 September 2012 in Budapest, Hungary. The Scientific Programme included 'clinical' and 'practical' track. The keynote lecture focused on personalized anticancer therapy, prominent themes included the expanding role of the oncology pharmacist and dose banding.

Introduction

From 27–29 September 2012, the European Society of Oncology Pharmacy (ESOP) held its first annual European Conference of Oncology Pharmacy (ECOP) in Budapest, Hungary. The meeting attracted more than 500 participants, drawn mainly from Europe—a total of 49 countries. The 10 most represented countries were Germany, Hungary, Austria, Italy, France, China, Spain, the UK, The Netherlands and Greece.

Mikael Daouphars
PharmD, PhD

Keynote lecture

The conference began with a keynote lecture on personalised anticancer therapy from Professor Martine J Piccart-Gebhart, former President of the European Organisation for Research and Treatment of Cancer, and President-Elect of the European CanCer Organisation.

Over the past decade, the complete sequencing of the human genome and the development of high-throughput processing methods have significantly advanced our ability to identify molecular alterations in individual cancers. These technological and biological discoveries, however, have not produced the same advances in cancer treatment.

In 2004, the translational research network of the Breast International Group launched a new research programme, with the objective of improving the tools used to evaluate the prognosis of breast cancer. Results showed that different gene expression prognostic signatures had similar prognostic performance if not higher than currently used risk-assessment tools, e.g. *Adjuvant! Online* [1].

The challenge for women who need treatment because of their high risk of relapse is selecting the best treatment at an individual level. In an attempt to generate level I evidence on the utility of the 70-gene classifier *MammaPrint* in routine clinical practice, the MINDACT trial [2] has recruited more than 6,600 participants, with final results to be published soon.

Targeted drugs' use could be optimised in the future by changing their clinical development: moving from initial activity demonstrated in unselected patients with advanced refractory disease, and subsequent retrospective biomarker discovery and validation in adjuvant therapy, to the discovery and validation of predictive biomarkers into earlier phases of drug development in neoadjuvant therapy, e.g. NeoBIG programme [3].

Professor Dr Dieter K Hossfeld, former President of the Federation of European Cancer Societies and the European Society for Medical Oncology, spoke about his personal experience of the field of medical oncology, which has spanned 50 years. His career began in the 1960s, when a diagnosis of cancer was hardly mentioned to the patient, and few, if any, cytotoxic drugs were available.

By the 1980s, many chemotherapy drugs had been discovered, with the growing hope that cancer could be defeated. Despite good results being achieved in child leukaemia, the reality is that we still struggle to cure all cancers. A new era has arisen with targeted therapies: future challenges are to personalise anticancer drugs to the tumour and also to the patient.

ECOP 2012 Scientific Programme

To cater for the educational needs of all participants, the ECOP 2012 Scientific Programme was divided into two separate

Mr Klaus Meier gave the opening speech at ECOP 2012

Professor Martine J Piccart-Gebhart, President of the European Society for Medical Oncology

tracks: clinical and practical. The conference has been granted recognition for continuous medical education by the Accreditation Council of Oncology in Europe and the EU of Medical specialists/European Accreditation Council for Continuing Medical Education.

Clinical track

One of the clinical sessions was dedicated to oral chemotherapy. This topic presents a major challenge to healthcare professionals in treatment adherence and self-management of side effects. Oncology pharmacists have the opportunity to play a crucial role in patient education programmes, provided that they can demonstrate adequate training in particular communication skills.

Dr Debbie Wright presented the clinical experience of oral chemotherapy at Southampton Oncology Centre, and Professor Ulrich Jaehde showcased positive results of oral chemotherapy adherence of pharmacist-led interventions.

Another clinical session provided insights into the innovative roles and responsibilities of pharmacists within the healthcare team. One example, discussed by Ms Fiona MacLean, is the extended prescribing rights given to oncology pharmacists in the UK. Dr Klaus Ruberg paid tribute to the pivotal role that community pharmacists play in the continuity of patient care, and elaborated on the German programme under way.

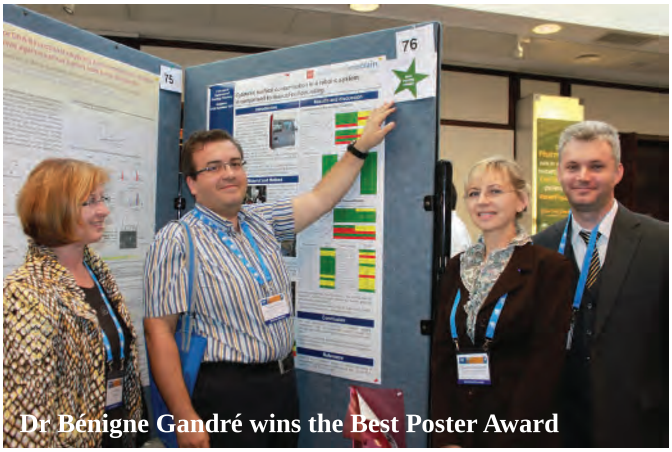
Pharmacovigilance is also increasingly considered essential to patient safety, and recent European guidance was detailed by Ms Doris Haider.

In recent years, the rising cost of oncology drugs has caused significant concern among government and healthcare agencies, healthcare providers and patients. Consequently, more sophisticated measures are being used by healthcare systems to address this. For oncology pharmacists, this has resulted in greater decision-making responsibility, e.g. in patient access schemes and health technology assessment. The oncology pharmacist's role in accessing new high-cost cancer drugs was discussed in a special session involving European experts from Italy (Dr Andrea Messori), Spain (Dr Ana Estela Clopes) and the UK (Ms Jackie Turner).

Practical track

The practical track included an in-depth discussion of physicochemical stability issues in cytotoxic drugs and monoclonal antibodies, drawing on the work of French experts, Professor Alain Astier and Dr Jean Vigneron; results of stability studies were presented either as oral communications or posters.

New data were presented on eribulin, bortezomib for SC injection, or rituximab stability in conjunction with pneumatic conveying systems. A debate-based session on dose banding gave specialists in the field of chemotherapy preparation and dose banding the opportunity to present their case in



Dr Bénigne Gandré wins the Best Poster Award

favour of or against dose banding in an attempt to convince the audience.

Professor Graham Sewell, worldwide recognised expert in dose banding; and Professor Etienne Chatelut, who presented pharmacokinetic data, were challenged by Professor Christian Dittrich and Mr Klaus Meier. Although practical feasibility evidence and pharmacokinetic results support the dose banding approach, clinical data are still needed before rolling it out to clinical practice.

The oncology pharmacist plays a central role in optimising the preparation processes and endorsing adequate procedures, e.g. safe handling. This topic was discussed in a 'Meet the Experts' session with Professor Robert M Mader, Mr Thomas Hinrichs and Ms Ewelina Korczowska.

Progress made in the last decade has led to new standards being set in the handling of cytotoxic agents. These improvements were based on (1) a deeper understanding of the critical steps in the handling procedure workflow; and (2) technical developments of devices that help improve the safe handling of anti-neoplastic agents.

In parallel, several monitoring studies have helped to identify weak points in our system, and stress the relevance of ongoing research in this field. Preparation robots are among the new technologies recently introduced to the field of chemotherapy preparation. Advantages of this new technology include less staff exposure to cytotoxic drugs, and the potential diversion of human resource to other activities.

Among the experts presenting on developments in automation were Dr Robert Terkola, who talked about PharmaHelp, and Professor Vagn H Handlos, who focused on Cytocare robots. The Best Poster Award was granted to Dr Bénigne Gandré from Professor Irene Krämer's team, on his work on cytotoxic surface contamination in a robotic system compared with compounding. More than 80 posters (over 123 submitted) were presented at ECOP on practical, clinical or research studies; abstracts were highlighted as oral communications or poster discussion forums.

The role of the oncology pharmacist has expanded in recent years to include the analysis of error medication and prevention. Contributors to this topic included Ms Doris Haider and Ms Stravoula Kitiri. Dr Roman Gonec also presented how radiofrequency identification technology can help secure preparation and administration of chemotherapy.

Closing session

At the closing session, Dr Gabor Pogany, President of HUFERDIS (Hungarian Federation of People with Rare and Congenital Diseases), on behalf of Professor Louis Denis from Europa Uomo, shared some patient expectations from oncology pharmacy. Along with our duties in preventing medication errors and drug interactions, quality control, and preparation of prescription drugs, patients would like pharmacists to feel responsible for the information, education and counselling of cancer patients, as they would expect from the medical and nursing community.

Dr Gabor Pogany, President of HUFERDIS, delivered the closing speech

Klaus Meier Award

Finally, a lifetime achievement award was offered to Mr Klaus Meier, President and Founder of ESOP.

In recognition of an ESOP member who has made a significant or sustained contribution to oncology pharmacy practice, it was announced that a 'Klaus Meier' Award would be created and granted at the next ECOP meeting in 2014. I encourage you all to attend.

A lifetime achievement award for Mr Klaus Meier, President and Founder of ESOP

Special thanks to ECOP 2012 Scientific Programme Committee

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This short overview of ECOP 2012 will be covered more extensively in future issues of EJOP, as the editorial office has invited some authors to present a report article, so that ESOP members who could unfortunately not be present at this special event, can nonetheless benefit from the information. ECOP Best Poster Award winners will present their work in future EJOP issues. Other ECOP authors are of course welcome to submit their results to EJOP editorial committee.

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Clinical pharmacy interventions in oncology

Medication errors can lead to inappropriate use or harm, and can occur anywhere along the prescribing continuum. The pharmacist can play an important role in evaluating and reporting errors, and developing quality-improvement programmes [1], this can reduce the number of medication errors.

Stavroula Theophanous-Kitiri, MSc

Introduction

A medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer [2]. Such events may be related to professional practice, healthcare products, procedures, and systems. They include prescribing, order communication, product labelling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Cancer drugs are involved in 15.4% of reported fatal cases [3]. High-risk drugs have serious consequences, including death; however, medication errors made in prescription preparation and administration also have serious consequences.

In addition to chemotherapy drugs, people with cancer receive multiple drugs that predispose them to many drug–drug interactions and adverse drug events [4]. Even though clinical pharmacists are actively involved in patient care, many of their efforts remain undocumented, resulting in an underestimation of the importance of their services and missed opportunities for improvements and new directions [5].

Medication errors can occur at any time, from the initial prescription order to the final consumption of the drug by the patient. Reports of medication errors and interventions should be evaluated and incorporated into a continuous quality improvement programme. The pharmacist must assume responsibility for developing and implementing a plan, and preventing medication errors through detection and evaluation.

The aim of drug treatments is to achieve defined therapeutic outcomes that improve a patient's quality of life while minimising risk. Around one in 10 hospital prescriptions, however, contain an error. Research has found that these errors can be minor or potentially lethal. A UK study commissioned by the General Medical Council in 2009 found that few errors would have caused serious harm [6]. A total of 124,260 prescriptions were checked by pharmacists in 19 hospitals in England, 11,077 (around 9%) errors were detected. The mistakes included omitting drugs, incorrect doses, patient allergies not taken into account, illegible handwriting, or ambiguous orders. It is not known how many errors were not picked up by the pharmacist, and so the figures are at the lower end.

When doctors were interviewed about their mistakes, some admitted that they relied on the pharmacist to correct them. Of these 11,077 errors were intercepted and corrected before reaching the patient, about 2% contained potentially lethal instructions, e.g. failing to account for a patient's allergies.

According to CHKS, the UK's leading independent provider of healthcare intelligence and quality-improvement services, patient drug allergies have recently been added to the prescription form. The doctor has to indicate on the form one of the following: whether the patient has an allergy; the name of the medication; if they do not have an allergy; or whether it is unknown whether or not they have an allergy. Not all doctors complete the allergy section on the prescription form.

The General Medical Council found that newly qualified doctors were twice more likely to commit a prescribing error than a consultant. Contrary to belief, more recently qualified doctors were no more responsible for perpetrating errors than experienced doctors. Doctors in their first year of medical training, however, made slightly fewer mistakes than average,

Figure 1: Interventions made by pharmacists in routine practice

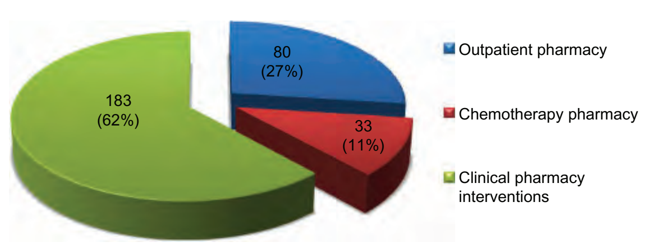
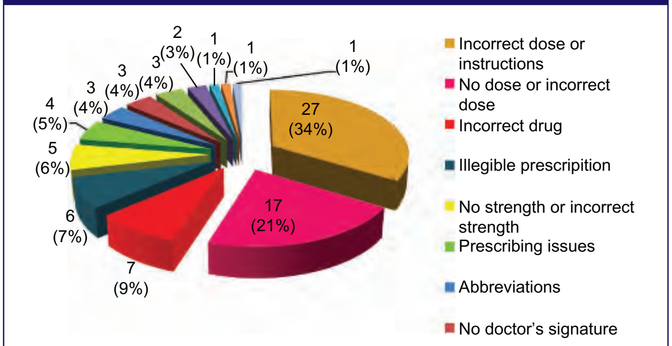


Figure 2: Errors made by clinicians in prescribing



although the error rate rose slightly in their second year; consultants, however, made the fewest mistakes. The General Medical Council has called for the establishment of a UK-wide prescription chart to reduce errors.

Few of these mistakes were found to cause actual harm to the patient, because the errors were intercepted by senior doctors, nurses and, in particular, pharmacists. Concerns were raised that some doctors relied too heavily on this safety net for picking up errors.

Opinion polls consistently show that pharmacists are one of the most trusted professionals—coming a close second to fire fighters (poll for the *Readers Digest*) [7].

Pharmacists are experts in medicines and have more in-depth knowledge about them than any other healthcare professional. The increased complexity of medicines, and the huge potential for medicines to interact with each other, makes prescribing more difficult. It is estimated that 5% of all hospital admissions are the result of adverse effects of medicines [8]. All of this means that doctors need support from pharmacists to help them improve prescribing, and patients need support to better understand and benefit from their medicines.

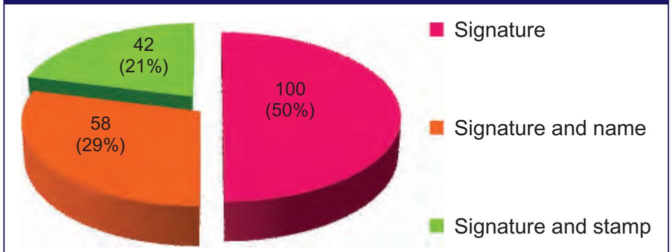
In hospitals, pharmacists are already an integral part of the clinical team, and advise on complex medicine regimens. Most prescribing, however, is started in the community, and it is here that pharmacists could play an important role in optimising therapy and avoiding adverse effects.

Pharmacy interventions at the Bank of Cyprus Oncology Centre

Methods

We conducted a study at the Bank of Cyprus Oncology Centre, a tertiary cancer centre. The aim of the study was to describe, evaluate and document the prevention of medication errors by clinical pharmacy interventions in people with cancer. We evaluated interventions made by pharmacists during their daily routine practice in the chemotherapy-dispensing pharmacy and outpatient dispensary, and during ward visits by clinical pharmacists. All medication errors detected by pharmacists were reported according to our departmental pharmacy procedure. Only the reported interventions that occurred between February and May 2012 were reviewed and analysed accordingly.

Figure 3: Doctor's data in opioid prescriptions



A documentation template was designed to collect the following information: patient data, supportive care issues, drug-specific interventions, and prescriptions written.

Results and discussion

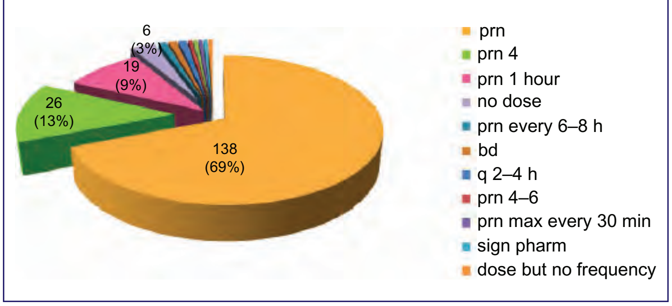
Pharmacy interventions included detecting medication errors in the outpatient dispensary, detecting chemotherapy errors during the verification of the prescribed chemotherapy regimen, and detecting inpatient errors during clinical pharmacist visits on the ward. The interventions were made by seven pharmacists—two clinical pharmacists on the ward and five pharmacists in chemotherapy and outpatient pharmacy. Not all pharmacists reported the same number of interventions. In total, 296 interventions were made by pharmacists. From these, 183 (62%) were clinical pharmacy interventions on the ward, 80 (27%) were pharmacy interventions in the outpatient pharmacy, and 33 (11%) were interventions in the chemotherapy pharmacy, see Figure 1.

Outpatient pharmacy

Pharmacists are rightly paranoid about accuracy because the consequences of an error could be serious. Most dispensing involves picking the right pack of medicines off the shelf and putting the right instructions on it. It is a manual task crying out for some form of automation. It involves manually entering information from a prescription into the pharmacy computer so that a label can be generated for the medicine. An electronic prescription could be automatically transferred from the doctor directly into the pharmacist's computer like e-mail, and could be used to automatically generate a label. Like most projects, the electronic prescription service is depressingly slow to deliver [9]. Supermarkets revolutionised check out throughput and accuracy with the use of bar-code scanners. But pharmacists cannot use them in dispensing because no industry standard bar-code system is in use across all manufacturers.

Between one-quarter and one-third of all prescriptions require strips of tablets to be cut, because the quantity on the prescription does not match the pack size. In most cases, if felt appropriate, the pharmacist will round up or round down the quantity to the nearest pack size for patients on long-term medication; it would make no difference.

Figure 4: Prescribing of morphine for breakthrough pain



At the Bank of Cyprus Oncology Centre, we dispense around 180 prescriptions and around 12 opioid prescriptions a day.

A total 3,772 outpatient prescriptions were dispensed during the period February to May 2012. During that period, 80 (2.12%) pharmacy interventions were reported by pharmacists as a result of detecting a medication error on the prescription, see Figure 2. Not all interventions were reported by pharmacists.

Twenty-seven (34%) prescriptions involved errors in which no dose or an incorrect dose or instructions were prescribed; in 17 prescriptions (21%), the patient's name or registration number was missing from the prescription. Seven (9%) prescriptions contained an incorrect medication, e.g. tamoxifen instead of anastrozole. These errors were identified by pharmacists through patient medication history available on our custom-made pharmacy software.

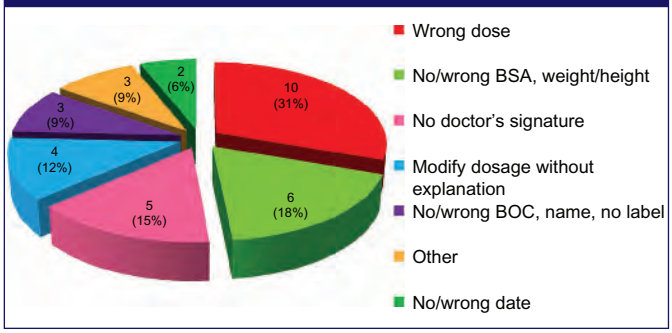
Other errors on prescriptions included illegible writing, ambiguous wording, or use of abbreviations, e.g. TMZ, TMX, and HCTZ. In all cases, the pharmacist contacted the doctor who made the correction on the prescription.

Although only two interventions were reported by pharmacists for narcotic prescriptions during the above period, more errors were identified after a random retrospective analysis of 200 prescriptions. According to Cyprus legislation, all prescriptions must be in the prescriber's own handwriting and include the patient's name, registration number, strength and form, total quantity of dose units written in words and figures, the dose to be taken by the patient, the prescriber's signature, and date. In 100 out of 200 (50%) of the prescriptions, only the signature of the doctor was on the prescription, which was difficult to decipher; 58 out of 200 (29%) of the prescriptions had both signature and the name of the doctor; and 42 out of 200 (21%) of the prescriptions had both stamp and doctor's signature, see Figure 3. The prescribing of immediate-release morphine was checked in 200 opioid prescriptions. In 138 (69%) of the prescriptions, an as-needed dose of morphine was prescribed without defining the frequency of administration of morphine; in 26 (13%) the doctor prescribed an as-needed dose of morphine to take up to every 4 hours; in 19 (9%) an as-needed dose of morphine was prescribed to take up to every 1 hour; in 6 (3%) the dose and frequency was not written by the doctor; in two prescriptions the frequency was every 12 hours and; in others, every 2–4 hours, every 4–6 hours, every 30 minutes; and one prescription was for mouthwash use, see Figure 4. From the above results, we assume that not all medication errors were detected or reported by pharmacists.

Chemotherapy pharmacy interventions

In collaboration with medical oncologists, clinical pharmacists are responsible for developing and amending all pre-printed chemotherapy prescriptions. We have a pharmacy department adjacent to our clean room. The pharmacists check all written chemotherapy prescriptions and ensure that the appropriate

Figure 5: Chemotherapy pharmacy interventions



time between treatment cycles has lapsed, appropriate antiemetics are prescribed, and specific toxicity-limiting steps are prescribed. Drug doses are calculated correctly according to body surface area. Then, the pharmacist defines the final dose by adjusting the dose up to 5% according to the quantity of drug in vials, thus making cost savings. Appropriate diluents and volume for reconstitution of powder forms and drug volumes are calculated, and the pharmacist signs the prescription. A total of 1,063 chemotherapy protocols were checked and doses dispensed accordingly during the above period. Thirty-three (3.1%) interventions were reported, which is less than expected. An incorrect dose was prescribed in 10 (31%) protocols; in other cases, chemotherapy was prescribed for a non-intended patient; a doctor's signature was missing; patient data, such as name, registration number, body surface area, weight or height, were either incorrect or missing, see Figure 5. In some cases, the dose was modified without any explanation, e.g. liver failure. All interventions were accepted and corrected by the doctors [10].

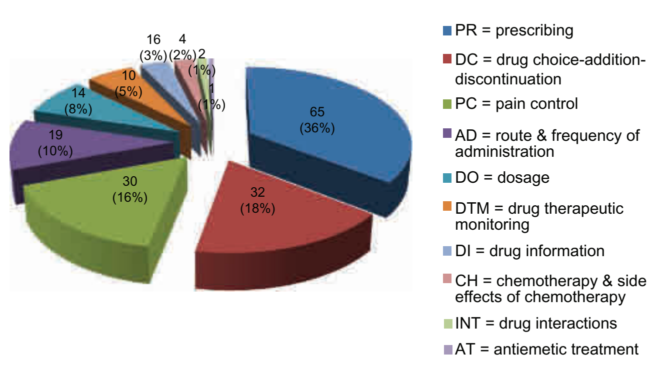
In one case, epirubicin instead of doxorubicin was administered to one patient, despite all checks taking place, e.g. doctor, pharmacist, nurse. An important distinction is needed when drugs that sound alike, e.g. doxorubicin and epirubicin are used for the same tumour types, and may be given to patients sitting next to each other in a busy infusion centre, but have significantly different dosing regimens and toxicity profiles [11].

Additionally, a decimal point can be missed if the prescriber fails to round doses of more than 5 mg or 10 mg to the nearest whole number, which can potentially cause a 10-fold overdose. Similarly, the unwise use of a 'trailing zero' or 'leading decimal' also has the potential to cause a 10-fold dosage error [12]. Computer systems may be the best prevention for medication errors; however, most oncologists still hand write orders, often because commercially available software simply is not available [13]. When it is available, it is often poorly written, incompatible with existing computer systems, or otherwise unreliable. As a result, other safety steps remain valid [14].

Clinical pharmacy interventions on the ward

Clinical pharmacists participate in ward rounds at the Bank of Cyprus Oncology Centre. They are members of the

Figure 6: Ward clinical pharmacy interventions



multi-professional team for supportive care of the hospital and the pharmacy and therapeutics committee.

During patient visits, supportive care issues were addressed, including pain management, constipation and diarrhoea, and nausea and vomiting. Major drug-specific interventions included drug addiction and discontinuation, and dose adjustment. On the ward, clinical pharmacists reviewed the patient's treatment charts and conducted patient interviews to obtain medication history. Identified drug-related problems were discussed with doctors, and appropriate interventions were made. Patient outcomes were evaluated by patient interviews on the following clinic visit or by follow-up telephone calls. All interventions were documented in pharmacy-documentation forms. Most interventions were unrelated to chemotherapy. The most frequent activity was patient counselling, followed by therapeutic recommendations after discussion and acceptance by the doctor. Most frequent interventions included pain control, drug addiction or discontinuation, dosage modification, and prescribing issues, see Figure 6. Other interventions included drug interactions, route and frequency of administration, therapeutic drug monitoring, extravasation, antiemetic treatment, and drug information.

Problems in prescribing [65 (36%)] documented on drug-therapy sheets, included use of drug abbreviations, prescription of drugs with their trade instead of generic name, drug prescriptions by junior doctors that needed authorisation from consultants, incorrect route of administration, doses written in milligram (mg) instead of microgram (mcg), administration of a non-prescribed drug and incorrect drug formulation.

Clinical pharmacists participate in pain management and palliative care. They discuss and recommend advanced analgesic administration methods, alternative drugs, and also help doctors with opioid conversion calculations. Many patients must switch from one opioid to another or from one route of administration to another as they approach the end of life, owing to either poorly controlled pain or the development of adverse effects. The management of adverse effects is a critical part of good pain management, and includes anticipating and preventing adverse effects. On the ward, clinical pharmacists recognise the importance of educating patients and caregivers about the therapeutic goal, analgesic regimen, and the management of adverse effects.

Recommendations on pain management [30 (16%)] included increasing or decreasing the dose of opioids and changing medication, e.g. from morphine to oxycodone, oxycodone to fentanyl. Furthermore, clinical pharmacists check all prescribed doses and conversions of opioids, and ensure that laxatives and hourly as-needed dose for morphine is prescribed for breakthrough pain. Patients were encouraged to ask for their breakthrough dose of morphine when in pain up to every hour. As-needed doses should not be given more often than hourly without medical review.

As pain has associated spiritual and psychosocial symptoms, clinical pharmacists referred patients to the spiritual priest and psychologist, who are members of our multi-professional team.

A pain diary and a pain scale were given to some patients to monitor pain levels, medication requirements, the effectiveness of analgesia, and any side effects. The effectiveness of a pain diary will be evaluated and introduced after the approval of the Pharmacy and Therapeutics Committee of the Centre. Clinical pharmacists will further contribute to the development of pain guidelines in the near future.

Clinical pharmacists reviewed medications through the use of a medication chart, and recommended discontinuation of the medication that was no longer indicated, e.g. azithromycin, ondansetron, lactulose, senna, metoclopramide. The recommendations were accepted by doctors. A new medication was added in some cases, e.g. omeprazole. Interventions were also made for the route of administration (oral or IV) and the time of day the drug was due to be administered. Proposals were made for dose reduction owing to a drug-related side effect or interaction. Appropriate dosing adjustment was recommended according to drug levels of drugs with narrow therapeutic index, such as vancomycin, gentamycin, carbamazepine, digoxin and phenytoin. Information was given to medical staff about specific side effects of chemotherapy, extravasation, handling of oral chemotherapy drugs, management of rash from cetuximab, and management of vomiting in specific

cases. Information was also provided about the prescribed dose of medications, such as prochlorperazine, lorazepam, and ranitidine. Also, information was provided to nursing staff about the reconstitution, storage and administration of medicines.

Conclusion

Pharmacy interventions among people with cancer can reduce the number of medication errors. All staff need to be encouraged to report medication errors [15]. The goal is not to blame a person but to improve the healthcare system, to reduce medication errors, and to improve the patients' quality of life. Strong evidence shows that, when appropriate education training is delivered, prescribing improves [16]. Procedures should be as simple as possible, to minimise the chance of an error being made.

Clinical pharmacists have a significant role to play in the management of people with cancer, and should be members of multi-professional teams of each hospital. Pharmacy input can lead to a decrease in healthcare costs and to an improvement of the quality of patient care [17]. Interaction with the healthcare team in patient rounds, identification of drug-related problems, and provision of information to patients and clinicians, can result in an improved outcome for the patient and hospital.

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The pharmacovigilance pharmacist in the service of the patient

Doris Haider, MBA, aHPh

The new good pharmacovigilance practice legislation aspires to excellent protection and promotion of public health and offers a rare opportunity to strengthen and rationalise public health; however, full and effective implementation will require major work [1].

Introduction

All medicinal products in the EU are subject to strict testing and assessment of their quality, efficacy, and safety before being authorised. Once placed on the market, they continue to be monitored to ensure that any aspect that could affect the safety profile of a medicine is detected and assessed, and that necessary measures are taken. This monitoring is called pharmacovigilance.

Good pharmacovigilance practice

Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines. It is a key public health function [2].

The EU pharmacovigilance system

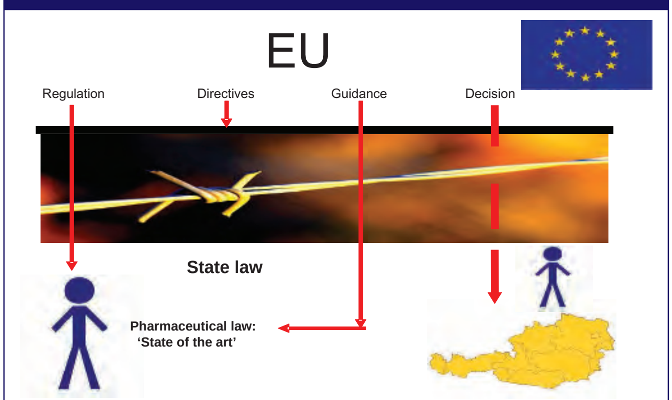
The EU pharmacovigilance system is now one of the most advanced and comprehensive systems in the world, and is a robust and transparent system that ensures a high level of public health protection throughout the EU.

The EU pharmacovigilance legislation was recently subject to a major review, and led to the implementation of new legislation in 2010. The new legislation, a 'regulation' and a 'directive' became applicable in July 2012.

Reasons for updating the system

The former EU pharmacovigilance legislation required updating to further strengthen pharmacovigilance. Statistics from EMA show that 5% of hospital admissions are a result of adverse drug reactions (ADRs); 5% of all hospital patients suffer an ADR; ADRs are the fifth most common cause of hospital death; an estimated 197,000 deaths per year in the EU are results from ADRs; and that the EU societal cost of ADRs are Euros 79 billion per year.

Figure 1: The scope of EU law



New legislation

The new legislation aims to promote and protect public health by reducing the burden of ADRs and optimising the use of medicines. This will be achieved through the delineation of clear roles and responsibilities; taking an evidence- and risk-based (proportionate) approach; increasing proactivity and planning; minimising duplication and redundancy; and integrating benefit and risk [1, 3].

In order to understand the pharmacovigilance legislation, it is important to define some of the terms used by EMA, as subtle differences exist between the terms, see Table 1. The scope of EU law is shown in Figure 1.

In a descriptive analysis evaluating prescription drugs withdrawn from the worldwide market between 1960 and 1999 [6], 122 medications were withdrawn because of safety issues; 44.1% with European licence. The most common drugs were central nervous system acting substances (31.4%); non-steroidal anti-inflammatory drugs (13.2%); and antidepressant drugs (7.4%).

The most common problems associated with these drugs were hepatic (26.2%); haematological (10.5%); cardiovascular (8.7%); and carcinogenic (6.3%). Two-thirds of the medications had been marketed for at least 5.4 years, and one-third had been marketed for only two years [6].

In June 2012, EMA published its first set of guidelines on good pharmacovigilance practices. Seven out of 16 modules were finalised, each covering one major process in the safety monitoring of medicines [7]. These are the recent modules:

Module I	:	Pharmacovigilance systems and their quality systems
Module II	:	Pharmacovigilance systems master files
Module V	:	Risk management systems
Module VI	:	Management and reporting of adverse reactions to medicinal products
Module VII	:	Periodic safety update reports
Module VIII	:	Post-authorisation safety studies
Module IX	:	Signal management

Table 1: Definition of terms used by EMA
Regulation: A legislative act of the EU that becomes immediately enforceable as law in all Member States simultaneously. Regulations can be distinguished from directives which, at least in principle, need to be transposed into national law [4].
Directive: A legislative act of the EU that requires Member States to achieve a particular result without dictating the means of achieving that result. It can be distinguished from regulations, which are self-executing and do not require any implementing measures [4].
Guidance: A published document, often by a regulatory agency, that contains a set of instructions, often to establish the publisher's expectations. They are often used to explain the objective or interpretation of a vague or non-specific law or requirement [4].
Decisions: On the basis of case law, decisions may have a direct effect, i.e. they may be invoked by individuals before national courts. Decisions may be addressed to Member States or individuals. The EU's standard decision-making procedure is known as 'co-decision'. This means that the directly elected European Parliament has to approve EU legislation together with the Council–the governments of the 27 EU countries [5].

Two further modules, i.e. Module III on 'Pharmacovigilance inspections' and Module X on processes for 'Additional monitoring' of medicinal products, were released for public consultation on 27 June 2012 and are envisaged to be finalized and published at the end of 2012 [8].

The remaining seven draft modules of the good pharmacovigilance practice package are under development, and were scheduled for an eight-week public consultation period during the third and fourth quarters of 2012, and will hopefully come into force at the beginning of 2013.

The new pharmacovigilance legislation also includes a modification to the definition of adverse reactions: a response to a medicinal product which is noxious and unintended. This is important for anyone working within the multi-professional team.

This includes adverse reactions arising from: (1) use of a medicinal product within the terms of the marketing authorisation; (2) use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors; and (3) occupational exposure.

A periodic safety update report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to competent authorities at defined time points after authorisation. These reports are expected to summarise information succinctly, and evaluate the risk–benefit balance of the product critically in the light of new or changing information.

A course will be available to delegates with a working knowledge of the changing ICH (International Conference on Harmonisation) Guideline E2C and the new EU legislation for the purposes of planning, writing and reviewing periodic safety update reports. Group sessions and workshops are included to address practical issues and application of the regulations.

EMA has also established a new scientific committee entitled, the Pharmacovigilance Risk Assessment Committee (PRAC) [9]. It is responsible for assessing and monitoring all aspects of drug safety in those drugs that have been approved in the EU. Its role will specifically affect national authorisations. Recommendations by PRAC are considered by the Committee for Medicinal Products for Human Use (for centrally authorised products) and the Co-ordination Group for Mutual Recognition and Decentralised Procedures–Human (for all other drugs). Its role, however, is purely advisory, and a thorough, public justification must be given for implementing any recommendations made by PRAC.

PRAC also assumes responsibility for referral procedures, approving post-authorisation safety studies, and coordinating the review of periodic safety update reports, which will in future be provided only by EMA.

The new Directive contains a transitional period for the introduction of the pharmacovigilance system master file, which will be concluded in July 2015. It is mandatory for all new marketing authorisation applications submitted after 2 July 2012 for centrally authorised products, and 21 July 2012 for all other authorisation types. New marketing authorisation applications must be introduced on renewal of products in the transition period. By the end of the transition period, pharmacovigilance system master files will have to be in place for all products authorised in the EU and the European Economic Area.

Conclusion

The new good pharmacovigilance practice legislation aspires to excellent protection and promotion of public health [1]. It draws on all relevant data sources, uses health data and epidemiology to support the drug lifecycle, and is evidence-based.

The new legislation offers a rare opportunity to strengthen and rationalise public health, however, full and effective implementation will require a great deal of work [1, 10].

For our patients, collaboration within the EU is the key [1].

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References can be found on page 31.

Nausea and vomiting during treatment with cancer drugs

Vomiting and nausea are the side effects most feared by patients following cytotoxic drugs and many perceive them to be especially unpleasant. If they are not adequately managed, cytotoxic drug treatment may be discontinued prematurely.

Professor Per Hartvig-Honoré, PharmD, PhD

Effective prophylaxis and treatment of nausea and emesis is fundamental in cancer. The effects of uncontrolled nausea and vomiting may significantly affect patients' overall treatment and response to treatment. Negative results for the patient are: dehydration, electrolyte imbalance, weight loss and malnutrition. Prolonged vomiting and retching can cause oesophageal and/or gastric rupture and bleeding. Patients with poorly-controlled nausea and vomiting often require interruptions or delays in treatment. There is also an increased risk of anticipatory nausea and vomiting hence noncompliance with the cancer treatment.

The symptoms are described as follows:

- Nausea - the feeling of an imminent desire to vomit
- Vomiting - the forceful upward expulsion of gastric contents
- Retching - attempts to vomit (also made using the diaphragm, chest wall and abdominal muscles)

Only a few years ago patients experienced severe, long-lasting nausea and vomiting following cytotoxic drug treatment. Today the situation is much better. Prophylaxis is used for emesis caused by cytotoxic drugs. A helpful discovery was that high doses of haloperidol or benzamides [1] were remarkably effective without significantly increasing the burden of side effects and a new era started in the treatment of cytotoxic drug-induced nausea and vomiting. The improved antiemetic effect was due to receptor interactions other than dopamine blockade. This finding started further investigation of the mechanisms causing cytotoxic drug-induced emesis [2].

The emesis following cytotoxic drug administration occurs in different phases. This is highlighted in treatment schedules for cytotoxic-induced emesis. Treatment is different in different phases of emesis. Choices can be made depending on the potency of different cytotoxic drugs to induce nausea and vomiting. Experts have contributed clinical experience to form the Perugia guidelines [3] and Multinational Association of Supportive Care in Cancer (MASCC) recommendations [4] which are updated regularly. Today there are no longer any differences between the Perugia guidelines and MASCC recommendations [5], see Table 1. Management of nausea and emesis should be instituted before cytotoxic drugs or other procedures causing nausea and emesis are started.

The acute phase starts some hours after drug administration and lasts for one to two days. Setrons block these symptoms by acting on serotonin 5HT3 receptors. Most setrons have a flat dose-response curve which means that finding the best dose is difficult, but otherwise the effects on acute emesis following cytotoxic drugs are dramatic. This class of drugs has become first-line treatment as prophylaxis for moderately to strongly emetogenic cytotoxic drugs and treatment in the acute phase of emesis. The acute emesis phase is thought to be due to cytotoxic drug-induced release of serotonin and other neurotransmitters from the chromaffin cells in the fundus of the ventricle and in cells close to the vomiting centre. Selective blockade of these receptors

Table 1: Consensus recommendations for prevention of cytotoxic drug-induced emesis [5]

Cytotoxic emetogenic potency	Cytotoxic treatment	Antiemetic treatment
Acute phase		
Low	5FU, methotrexate	Dexamethasone
Moderate		Palonosetrone + dexamethasone
High	Cyclophosphamide + anthracycline	Setrone + dexamethasone + aprepitant
Other high-potency drugs	Epirubicin, cisplatin carboplatin	Setrone + dexamethasone + aprepitant
Delayed emesis		
Low		No prophylaxis
Moderate		Dexamethasone
High	Anthracyclines + cyclophosphamide	Aprepitant
High (others)	Other than anthracyclines + cyclophoshamide	Dexamethasone + aprepitant
Anticipatory emesis		
		Prevention of acute and delayed emesis (lorazepam)

explains the success of the 5HT3 receptor-blocking setrons. It is now realised that the effect does not block nausea and vomiting effectively for more than one to two days after cytotoxic drug administration. New setrons, e.g. palonosetron, which are eliminated slowly and have a higher affinity for 5HT3 serotonin receptors, offer some advantages but it is still obvious that the effect wears off after a few days [5].

Delayed emesis starts on day two to three and persists for up to a week. The setrons are not very effective. Instead, combinations of dopamine receptor blockers and steroids are used. The origin of delayed emesis is difficult to explain. One theory of the origin of cytotoxic drug-induced emesis was put forward in 1988 [3]. Delayed emesis requires explanation since at the time of its development the cytotoxic drugs and their metabolites have usually left the body [2]. It has been suggested that cytotoxic drugs also attack DNA in other types of cells, e.g. in cells that form enzymes to degrade endogenous neuropeptides. These neuropeptides, known as enkephalins, release neurotransmitters such as dopamine and serotonin which in turn stimulate nausea and vomiting receptors. Cytotoxic drug inhibition of degradation enzymes limits catabolism and the neuropeptide concentrations increase causing emesis 2–3 days after cytotoxic drugs. This process continues until new DNA is formed in the enzyme-producing cells. This explains why symptoms persist so long after drug administration [2].

The metabolism of another neuropeptide, substance P, is regulated by amidases and esterases in the body and is similarly involved in emesis. The action of substance P is inhibited by selective substance P or neurokinin-1 receptor antagonistic drugs [2]. New drugs blocking the substance P receptors, e.g. aprepitant, have shown good effects on cytotoxic drug-induced delayed emesis and together with steroid drugs are suggested as first-line treatment for cytotoxic drug-induced delayed emesis. In fact, the effect of aprepitant is only valid after the enkephalin concentrations have built up which may become apparent as nausea and vomiting symptoms first on the second day after cytotoxic drug administration. So administration of these drugs may start later but usually today they are given from the start of cytotoxic drug treatment.

Anticipatory emesis occurs after several cycles of cytotoxic drug administration. The anticipatory effects appear long after drug administration and sometimes even before drugs are given. The symptom is caused by sensitisation to nausea in the nerve tracts and is difficult to treat. Anticipatory nausea and vomiting are likely due to the opening of calcium channels in the N-methyl-D-aspartate receptor complex in the vomiting centre in the area postrema occurring in the brain during strong nausea and vomiting [2]. Opening activates these cells and stimulates C-fos mRNA to form 'memory protein' a long time after drug therapy. C-fos is a family emanating from what is known as 'intermediate early genes'. These genes are present in many tissues but usually at very low concentrations. Various stimuli trigger increased C-fos mRNA within minutes and it persists for between minutes and weeks. The protein produced by C-fos is a regulatory protein and controls target gene expression. The mechanism by which external stimuli are converted into long-term changes within the cell is also suggested to occur in hyperalgesia and post-traumatic stress syndrome. The setrons are able to minimise the most intense symptoms for nausea and vomiting and C-fos formation is hence diminished. Effective treatment of the early phases of emesis will help but the amnesia effect of benzodiazepines, e.g. lorazepam also helps decrease anticipatory emesis.

Hands-on support for the clinical oncologist in the individualised prescription of antiemetic drugs following cytotoxic drugs is recommended [3-5]. It may be possible to individualise treatment to reach acceptable symptom control. The guidelines classify different cytotoxic drugs and drug regimens with respect to severity and duration to suggest optimised management. Still, patients suffer from nausea and hence there is need for further improvements. It is also obvious that nausea and vomiting are different entities where emesis is in fact easier to treat successfully. The mechanisms of cytotoxic drug-induced nausea and vomiting, which differ from other causes of emesis, are still to be fully understood and properly used to develop drugs for more effective treatment.

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Managed-entry agreements as a way of enabling patient access to innovation

Paolo Daniele Siviero, BA

Conditional reimbursement schemes between pharmaceutical companies and purchasers have been pioneered by the Italian Medicines Agency (AIFA). This article provides an insight into the aims of AIFA's 'managed-entry scheme', the approaches used, and tools developed to achieve its objectives.

At the 24th Drug Information Association Annual EuroMeeting held in Copenhagen, Denmark, 26–28 March 2012, a presentation was made by the Italian Medicines Agency [*Agenzia Italiana del Farmaco*, AIFA] on managed entry agreements as a way of implementing outcomes of assessment and enabling patient access to innovation.

All healthcare systems face three important challenges: guaranteeing a patient's access to new treatments; coping with the uncertainty when deciding on pricing and reimbursement; and guaranteeing overall budget sustainability.

According to AIFA, in order to guarantee the affordability of innovative medicines, their usage must be linked with clinical outcomes obtained. Lack of evidence in real clinical settings, particularly for innovative medicines, has encouraged the agency to use conditional reimbursement schemes, termed 'managed-entry agreements', in line with the definition developed by the Health Technology Assessment International Policy Forum [1].

Italy is recognised as one of the pioneers in developing access schemes for new medicines. The prices of reimbursed innovative pharmaceuticals are usually associated with some form of conditional reimbursement agreement concluded by AIFA and pharmaceutical companies. The aim is to assure access to new medicines for all patients, maintain the pharmaceutical budget by using these innovative drugs in target disease populations, and avoid unnecessary expenses to the National Health Service.

AIFA has developed a wide range of approaches to manage the effect of new products and indications. Managed-entry agreements focus on managing the following: (1) the effect of new drugs on the budget; (2) the uncertainty of clinical or cost-effectiveness of a drug in a real-world setting; and (3) managing drug use for optimum performance, by targeting patients or using delivery mechanisms. The tools used by AIFA during the pricing and reimbursement process are presented in Figure 1.

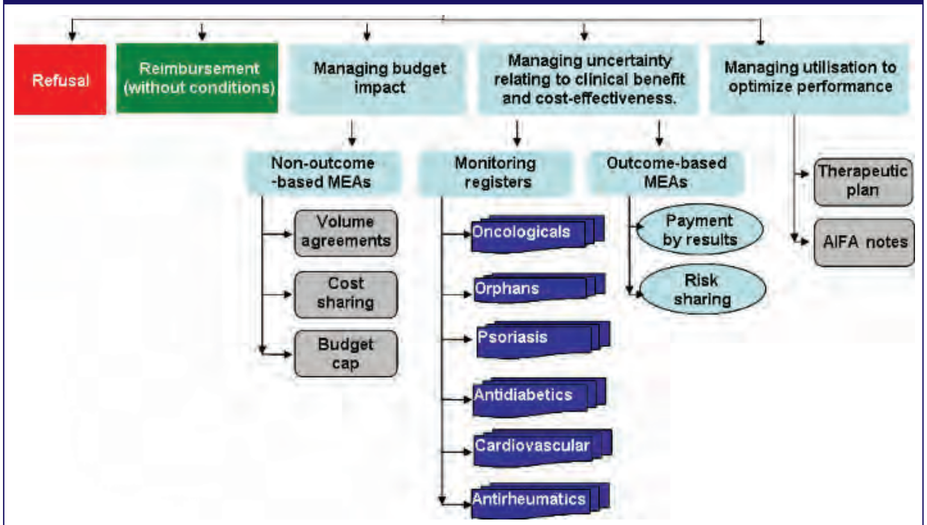
Managed-entry agreements can play a key role in accessing medicines in cases where uncertainties are related to the therapeutic benefits of medicines or where the costs of new medicines are high.

The AIFA monitoring registry is an important tool that is used when a conditional reimbursement agreement is drawn up. The registry tracks the eligibility of patients and the complete flow of treatments. This tool guarantees appropriate use of medicines according to their approved indications. Patients eligible for treatment with pharmaceuticals are registered in specific monitoring registries so that the effectiveness of treatment can be evaluated in clinical practice. Epidemiologic, safety profile, and ex-post evaluation data on any missing information is also added to the registry.

These tools have been used in different therapeutic areas, see Figure 1. The most populated registry is the oncology registry, accounting for more than 40 therapeutic indications. Overall, about 80 therapeutic indications are included in the different therapeutic registries.

Conditional reimbursement is linked to the success of therapeutic effectiveness. The agency uses three different ways to share responsibility and risk within pharmaceutical companies and the National Health Service (a third-party payer), see Table 1.

Figure 1: AIFA's managed-entry agreement



AIFA: Italian Medicines Agency; MEA: managed-entry agreement.

Table 1: Conditional reimbursement schemes – the Italian experience	
Type of conditional reimbursement scheme	**Description**
Cost sharing	A discounted price is given to the National Health Service (NHS) for the initial treatment cycle for all eligible patients.
Risk sharing	A discounted price is given to the NHS for the initial treatment cycle for patients who have not responded to the treatment.
Payment by results	The initial cycle is fully reimbursed by the marketing authorisation holder for patients who have not responded to treatments; treatments for patients who have responded are fully reimbursed by the NHS.

Risk sharing and payment by results are two typical performance-based agreements conditioned by clinical evaluation of specific end points, with limitations of cost if the effect is inappropriate. The validity of these agreements is for a limited time period, under specific conditions, waiting to be re-evaluated. The most used conditional reimbursement schemes are payment by results and cost sharing. These tools are also important for supporting decision-making for innovative medicines.

Thirty-three oncology products are in place with the monitoring registry; among these, 21 are subject to conditional reimbursement—out of the 26 therapeutic indications.

At the European level, interest in the development of such types of tools continues to grow. AIFA, on behalf of the Italian National Health Service [*Servizio Sanitario Nazionale*, NHS] is actively involved in a project funded by the European Commission entitled 'Capacity building on managed entry agreements for innovative medicines'. The project involves 19 European countries. All the countries agree that managed-entry agreements are valuable in helping to strike a balance between access to medicines and increasing costs.

The project has multiple objectives. These include: (1) collecting and analysing information about the managed-entry agreements used by the EU Member States to find a possible way of harmonising taxonomy; and (2) conducting a systematic analysis to support the decision-making process of competent authorities for reimbursement purposes. The findings could foster knowledge exchange among European Member States.

One of the expected outcomes from this project is to realise a sustainable collaboration between Member States and stakeholders to collect the expected information and produce the foreseen reports. This initiative is expected to improve the level of information on the different decision-making processes used in EU countries and to contribute outcome analysis.

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Guidelines for supportive care and rehabilitation in oncology: where are we in 2012

The ASORS working group of the German Cancer Society is drafting a set of guidelines on supportive care and rehabilitation for cancer patients that aim to be evidence-based and as comprehensive as possible.

Introduction

The Working Group for supportive Care, Rehabilitation and Social Medicine [*Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin*, ASORS] is a multidisciplinary working group within the German Cancer Society. ASORS members come from many different disciplines and medical societies.


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Guidelines are an important instrument for ensuring quality of care. In particular, guidelines for supportive care in oncology are the basis for managing side effects of the treatment and enable the treatment to be administered in the planned time and dose schedule. Thus, they are not only a supportive document for cancer treatment but also an essential part of the therapy itself, as a reduction in dosage or altered administration due to side effects reduces the effectiveness of the therapy.

Modern cancer treatment has fundamentally improved the cancer-free survival of patients and the overall survival for individuals with many types of tumour. This increasingly raises the issue of cancer survivorship and relates closely to the motto of the Multinational Association of Supportive Care in Cancer (MASCC) – *Supportive care makes excellent care possible*.

During and after cancer treatment supportive and rehabilitative therapies focus on interventional or prophylactic measures to manage side effects and help patients to recover from intensive therapeutic regimens. Although often in daily use, evidence-based guidelines for these therapies are rare and comprehensive guidelines for supportive care and rehabilitation in oncology do not exist.

Responding to this gap, ASORS has set up two interdisciplinary and multiprofessional projects to develop guidelines on the S3 (evidence-based) level:

- the S3 guideline for supportive care in cancer, created together with the German Society of Hematology and Oncology [*Deutsche Gesellschaft für Hämatologie und Onkologie eV*, DGHO] and the German Society of Radiooncology [*Deutschen Gesellschaft für Radioonkologie e.V.*, DEGRO]
- the S3 guideline on rehabilitation and social medicine, created together with the German Society of Rehabilitation Science.

To produce the S3 guidelines for supportive care in cancer, ASORS is working within the guideline progammes of the German Medical Societies and the German Cancer Society. As much as possible of these guidelines will be evidence-based, but as there is difficulty in setting up large randomized trials in this field, there will also be parts with expert consensus.

Summary of existing guidelines in supportive care

Anaemia

Both European Organisation for Research and Treatment of Cancer (EORTC) and American Society of Clinical Oncology (ASCO) have guidelines regarding anaemia dating from 2010 for ASCO. ASORS will decide whether to adapt existing guidelines or begin *de novo*.

Neutropenia and infection

ASORS plans to adapt existing guidelines concerning neutropenia from ASCO (2006) and EORTC (2011). Infections in cancer care can include febrile episodes of unknown origin, bacterial, viral or fungal infection, and sepsis or catheter infections. ASORS has yet to decide which of these problems to include in the new guideline. Of help is an algorithm for daily practice contained in the Working Group of Infections in Hematology and Oncology [*Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie*, AGIHO] guidelines.

Skin toxicity

There is no existing national or international evidence-based guideline on this issue. The MASCC study group on skin toxicities has worked out a clinical practical guideline (www.mascc.org). However, several topics are missing, including toxicity during (V)EGFR-therapy, hand–foot syndrome, alopecia, and reactions to other single agents like taxanes or bleomycin. *De novo* research therefore seems necessary.

Mucositis

The ASORS guideline will draw from existing documents relating to mucositis including a MASCC guideline from 2004. This

will need to differentiate between oral and gastrointestinal forms of mucositis as well as mucositis of other organs, such as vesical or vaginal mucositis. An algorithm for prophylactic and interventional treatment should be included in the ASORS guideline.

Paravasation/Extravasation
An ASORS guideline including case reports and expert consensus exists and has been submitted for publication. As an S-3 level guideline, this is expected to have legal consequences.

Venous thromboembolism
Existing guidelines from ASCO, DGHO, National Comprehensive Cancer Network (NCCN) cover this aspect of cancer-related disease. There is a need, however, for a 'bedside' algorithm for treatment or prophylactic anticoagulation.

Nausea and vomiting
MASCC/European Society for Medical Oncology (ESMO) and ASCO updated their evidence-based guidelines on these side effects in 2010/2011. The ASORS S3 guidelines will draw on these and the guidelines of the US NCCN on clinical practice which are regularly updated.

Neurotoxicity
In 2008, the German Association for Neurology [*Deutsche Gesellschaft für Neurologie*, DGN] established a guideline for diagnostic and therapeutic procedures in neurology. This included a chapter for neuropathy and neuritis, and reference to chemotherapy-induced peripheral neuropathy (CIPN). Even so, there remains the need for new guidance on the management of CIPN after different antineoplastic agents, although DGN may address this in the next update.

Radiotherapy induced toxicity
The DEGRO S1-guideline of 2006 has recently been updated and upgraded to S2e, which provides an opportunity to produce a further update for the S3-guideline.

Fertiliy protection
The FertiProtect strategy includes a useful algorithm but is apparently not evidence-based. Other than that there exist recommendations from ASCO and German Association for Gerontology and Geriatric Medicine [*Deutsche Gesellschaft für Gerontologie und Geriatrie*, DGGG], there are no guidelines.

Bone complications
German Gynaecology Oncology Group established a guideline that covers issues such as bisphosphonates, and surgical and radio-oncological management of bone metastasis. This contains an Oxford grading and a report of methods which could be adapted for the ASORS S3 guideline.

Management of cancer therapy
Cancer centres usually work with internal guidelines and standard operating procedures concerning their individual setting. A guideline would not mention each of these single centre specificities. Furthermore, due to the great variety of cancer therapies, certain issues would also be omitted. The management of cancer therapy is a topic that is likely to be covered in an update rather than in the first version of the guideline.

Rehabilitation and social medicine

Goals and challenges in rehabilitation and social medicine in oncology
The planned ASORS guideline for rehabilitation and social medicine will be an S3-guideline containing, as far as possible, evidence-based knowledge aimed at providers of rehabilitative therapies and those who apply or pay for the setting.

Traditionally rehabilitative therapies in Germany are offered in specialized rehabilitation centres, usually situated in picturesque landscapes where the traditional German spas arose, for example, at 'Bad' Nauheim, 'Bad' Wiessee or 'Bad' Kreuznach.

The aims of recreational therapies following cancer treatment focus on physical and psychological well-being. For a long while 'to rest' or 'relax' was one of the main elements in this setting. This has changed fundamentally during the past decade. Nowadays, rehabilitative treatment deals with issues such as returning to work and participating in social life. Rehabilitation is therefore now an integral part of the concept of cancer survival.

The oncological rehabilitative units offer a programme which holistically combines therapies to restore physical activity, as many cancer patients suffer from exhaustion and fatigue after treatment. Added to this is psychological support from specialized, psycho-oncological psychotherapists. Depending on the needs of patients, the rehabilitation treatment may also include physiotherapy, ergotherapy (occupational therapy), training in speech and swallowing, as well as a nutritional programme.

Rehabilitation is based on the International Classification of Functioning, Disability and Health, which focuses on functional deficits due to malignant disease and its treatment, compared to the International Statistical Classification of Diseases and Related Health Problems (ICD) which focuses on diagnosis. This includes a training programme in which activity, information and return of empowerment dominate rather than rest and regression.

For historical reasons, the cost of rehabilitation in Germany is usually covered by the retirement fund. If the client has not made sufficient payments into the retirement fund, their health insurance or other parties might cover the cost.

Access to rehabilitation depends on an individual's situation, needs and information provided, usually by social workers. Up to now about 20–30% of all cancer patients take advantage of rehabilitative treatment, while others may not due to lack of information or other reasons. It has therefore been impossible in the past to design randomized trials. Furthermore, it has been difficult to evaluate the effect of single therapies in rehabilitation, since the combination of physical training, education and psychological

support might together lead to an individual's rehabilitative success. For example, rehabilitation in other European countries or outside Europe differs with regards to time schedules and duration. In Germany, the patient is usually treated daily for three weeks in an inpatient setting whereas in other countries outpatient management with alternating therapy periods or 'days off' can lead to a much longer rehabilitation period.

The planned ASORS guideline for rehabilitation and social medicine will need to take these features into account and will evaluate existing guidelines for rehabilitative treatment.

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36th ESMO Congress report: practice changing studies and personalized treatment

The 37th Congress of the European Society for Medical Oncology (ESMO) held 28 September to 2 October 2012 in Vienna, Austria, was a record breaker on all levels. With 16,394 participants including 1,116 from the US, 539 from Japan, 292 from China and 550 from Argentina and Brazil.

The strong scientific programme benefitted from the submission of 2,200 abstracts – an increase of more than 30% since the previous ESMO Congress in 2010 – of which 1,239 were presented. There were over 50 late breaking abstracts submitted and data from 110 phase III trials were reported. The five-day event was comprised of two Presidential Symposia, several Joint Symposia with other professional and scientific societies, several special sessions, proffered paper sessions, and seven Young Oncologist sessions, together with 37 industry sponsored symposia.


Svetlana Jezdic, MD

A primary emphasis was placed on personalized medicine and how it will change the future landscape in oncology.

The key message delivered by Dr Josep Tabernero, Chair of the ESMO 2012 Scientific Committee was that personalized cancer medicine is becoming a reality in clinical work. Many of the presentations contained new information on biomarkers and several studies that used biomarker data to stratify patient treatment. Some of the results presented were practice changing and many others suggested new or alternative treatment options for patients.

The ESMO Scientific Committee has turned a watchful eye to the economic crisis and included topics such as the economic burden, both direct and indirect, of cancer in Europe, health economics, drug costs and the unsustainability of cancer care, which were presented and discussed by experts.

This report is an overview of representative scientific presentations made during the congress by premier international investigators. It attempts to represent the diversity and depth of the ESMO 2012 scientific programme.

Crizotinib superior to standard chemotherapy in patients with advanced ALK-positive non-small cell lung cancer

A randomized phase III study (PROFILE 1007) compared the efficacy and safety of crizotinib to standard chemotherapy with pemetrexed or docetaxel as second-line treatment for patients with advanced FISH-determined ALK positive non-small cell lung cancer (NSCLC). Over a two-year period, the study enrolled 347 patients with stage IIIB/IV, ALK+ NSCLC who had previously received one platinum-based regimen; 173 patients were randomized to crizotinib and 174 to either pemetrexed (58%) or docetaxel (42%). Patients who progressed on pemetrexed or docetaxel were offered crizotinib. The trial's primary endpoint was progression-free survival (PFS) per independent radiologic review, with secondary endpoints of objective response rate (ORR), overall survival (OS), safety and patient-reported outcomes. The study met the primary endpoint by showing crizotinib superiority over pemetrexed or docetaxel with a median PFS 7.7 months compared with 3.0 months ($p < 0.0001$). Patients treated with crizotinib also had a significantly higher ORR of 65.3% compared with 19.5% ($p < 0.0001$). An interim analysis of OS done at 28% events showed no statistically significant difference between crizotinib and pemetrexed or docetaxel. More patients receiving crizotinib over chemotherapy reported improvement in symptoms from baseline

of cough, dyspnoea, fatigue, alopecia, insomnia and pain, $p < 0.0001$. Improved global quality of life also favoured crizotinib, $p < 0.0001$. The most common treatment-related adverse events with crizotinib were vision disorder, which was reported by 60% of patients; 60% of patients reported diarrhoea, 55% had nausea, 47% vomiting and 36% of patients reported elevated transaminases. Adverse events including nausea, constipation, fatigue and rash were reported by 37%, 23%, 33%, 21%, respectively, and 17% of patients receiving pemetrexed or docetaxel (Shaw et al. Abstract # LBA1_PR).

Practice point and future research opportunities

Crizotinib may be considered the standard of care for second-line treatment of patients with previously treated advanced ALK positive NSCLC. Results from this study showed significantly improved progression-free survival, response rate and quality of life with crizotinib over pemetrexed or docetaxel. Lack of a difference in OS rates was most likely due to the immaturity of data at the interim analysis and to the large number of patients who crossed over to treatment with crizotinib.

A head-to-head comparison of pazopanib versus sunitinib as first-line treatment of patients with metastatic renal cell carcinoma

The randomized, open label, phase III COMPARZ (COMParing the efficacy, sAfety and toleRability of paZopanib versus sunitinib) trial was a head-to-head comparison of the efficacy, safety and tolerability of pazopanib versus sunitinib in 1,110 treatment naive patients with clear cell metastatic renal cell carcinoma and measurable disease. The patients were randomized 1:1 to receive either continuous pazopanib or sunitinib in 6-week cycles. The primary endpoint was PFS and key secondary endpoints included OS, ORR, adverse events, and quality of life. Patient characteristics were balanced between arms. The non-inferiority of pazopanib was demonstrated; the upper bound of the 95% confidence interval for PFS was less than 1.25. In 557 pazopanib treated patients versus 553 receiving sunitinib, the independent review committee and investigator determined median PFS rates were 8.4 vs 9.5 months, hazard ratio (HR) 1.0466 and 10.5 vs 10.2 months, HR 0.998, respectively. Median OS was 28.4 months with pazopanib and 29.3 with sunitinib, HR 0.93. The ORR favoured pazopanib at 31% compared with 25% in the sunitinib arm. The most commonly reported adverse events—reported by 40% or more patients—of diarrhoea, fatigue, hypertension and nausea occurred at similar frequency in both treatment arms. Hand–foot syndrome was reported by 29% of pazopanib and 50% of sunitinib patients; higher rates of dysgeusia, dyspepsia, hypothyroidism, mucositis, thrombocytopenia and neutropenia were also seen in the sunitinib arm. More patients in the pazopanib arm showed liver function adverse events; 33 vs 18 showed elevated ALT (HR 1.74) and 31 vs 25 showed elevated AST (HR 1.49) than with sunitinib. Differences in 11 of 14 quality of life domains, all favouring pazopanib, were reported but the minimally important difference was not met (Motzer et al. Abstract # LBA8_PR).

Practice point and future research opportunities

Pazopanib demonstrated non-inferiority to sunitinib as first-line treatment of patients with clear cell metastatic renal cell carcinoma with a more favourable safety profile and improved patient reported quality of life domains.

Continuation of bevacizumab beyond progression improves survival in patients with metastatic colorectal cancer

A phase III study conducted by *Gruppo Oncologico Nord Ovest* (Italy) evaluated whether continuing bevacizumab with second-line chemotherapy beyond progression would improve survival in patients with unresectable metastatic colorectal cancer, as suggested by retrospective data. The trial randomized patients with metastatic colorectal cancer who had received bevacizumab plus first-line chemotherapy with fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI to receive a second-line chemotherapy using either FOLFOX or FOLFIRI alone (arm A) or together with bevacizumab (arm B). Patients were stratified according to centre, performance status (PS 0 vs 1–2), disease-free interval from the last administration of first-line chemotherapy (≤ 3 months vs > 3 months) and the second-line regimen. The primary endpoint was PFS. The trial was designed to randomize 262 patients but accrual was halted on 11 May 2012 when it was noted that the similarly designed AIO/AMG ML18147 trial showed improved OS with bevacizumab beyond progression. Prior to the early end, the trial had randomized 185 patients; 184 patients were included in the

intent-to-treat analysis. Arm A comprised 92 patients who were 75% male with a median age of 66 years; 82% of patients had PS 0 and 76% had disease at multiple sites; liver only disease was seen in 15% of patients. Patients in arm B were slightly younger with a median age of 62 but other characteristics were the same or similar to arm A. The study met the primary endpoint; at median follow up of 18 months there were 172 (93%) events for PFS and median PFS was 4.97 months for arm A chemotherapy alone patients compared to 6.77 months for arm B, chemotherapy plus bevacizumab patients, hazard ratio (HR) 0.65, p = 0.0062. A PFS analysis that adjusted for stratification factors, age and sex confirmed that bevacizumab added to chemotherapy improved PFS over chemotherapy alone, HR 0.70, p = 0.032. An increased response was also demonstrated in arm B with response rates of 18% for chemotherapy alone and 21% for chemotherapy plus bevacizumab, but the difference was not statistically significant. Overall survival data are not yet mature with arm A having 52 events and arm B having 46 events thus far. The adverse event profile was consistent with previously reported data for bevacizumab plus chemotherapy (Masi et al. Abstract # LBA17).

Practice point and future research opportunities

This is the second randomized, controlled trial to show continued bevacizumab plus second-line chemotherapy after progression improves progression-free survival in patients with metastatic colorectal cancer and may represent a new treatment option.

One year of adjuvant trastuzumab remains the standard of care for patients with *HER2*-positive early breast cancer

HERA was an international, multi-centre, phase III randomized trial that evaluated whether longer-term trastuzumab treatment would improve outcome of patients with *HER2*-positive early breast cancer. A total of 5,102 women were randomized, following completion of primary therapy consisting of surgery, chemotherapy and radiotherapy, as indicated, to observation only or trastuzumab every 3 weeks for 1 year or 2 years. The efficacy analysis compared the outcome of 1,703 women receiving trastuzumab for 1 year and 1,701 women receiving trastuzumab for 2 years who were disease-free at 1 year post-randomization. The primary endpoint was disease-free survival (DFS) and secondary endpoints included OS and time to distant recurrence. At 8 years of follow-up, DFS and OS in the two arms were comparable, with no significant difference between treatment duration; however, trastuzumab treatment for either 1 or 2 years showed a significant benefit compared to observation, despite selective crossover. The primary cardiac endpoint (cardiac death or severe congestive heart failure defined as a NYHA class III or IV, confirmed by a cardiologist, and a significant left ventricular ejection fraction - LVEF decrease) was comparable at 0.96% vs 0.83% but the secondary cardiac endpoint (defines as an absolute decline $\geq$ 10% points from baseline LVEF and to $<$ 50%) was 7.17% vs 4.10% for the 2 year and 1 year arms, respectively (Goldhirsch et al. Abstract # LBA6_PR).

Results from the recent FinHer study showed a similar magnitude of benefit obtained with 9 weeks of adjuvant trastuzumab as with 1-year treatment. Concerns of over-treatment and cardiac toxicity associated with trastuzumab led the French National Cancer Institute to initiate an academic, randomized, non-inferiority comparison of trastuzumab exposure of 6 months to the standard 12-month course. The PHARE (Protocol for Herceptin as Adjuvant therapy with Reduced Exposure) trial enrolled 3,382 patients with *HER2*-positive early breast cancer who had previously received at least 4 cycles of (neo)-adjuvant chemotherapy. The patients were randomized 1:1 using a minimization algorithm stratified by concomitant or sequential trastuzumab administration with chemotherapy, oestrogen receptor status and centre to receive trastuzumab for 6 or 12 months. The primary endpoint was DFS, and OS and cardiac toxicity were investigated as secondary aims. Disease and treatment characteristics were well-balanced between the arms. Patients had a median age of 55 years, median tumour size of 20 mm, node involvement was seen in 45% of patients, 56% of patients had Scarff-Bloom-Richardson grade III disease and 58% were ER-positive. In all, 88%, 58% and 73% of patients had received prior radiotherapy, concomitant trastuzumab administration and anthracycline and taxane containing chemotherapy, respectively. The median follow-up was 47.2 months. No significant difference was shown in DFS between 6 and 12 months of treatment, the hazard ratio was 1.28 (p = 0.29) (Pivot et al. Abstract # LBA5_PR).

Practice point and future research opportunities

One year of adjuvant trastuzumab remains the standard of adjuvant care for patients with *HER2*-positive early breast cancer. The response is durable and the incidence of cardiac events remained low at a median follow-up of 8 years in the HERA study. Non-inferiority of a 6-month regimen could not be demonstrated in the PHARE study.

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