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Which role shall the pharmacists play in oncology

Klaus Meier
Editor-in-Chief

EJOP

The European CanCer Organization (ECCO) describes itself as 'the driving European force in multidisciplinary and multiprofessional oncology', and as existing 'to uphold the right of all European cancer patients to the best possible treatment and care.'

Across Europe, cancer is now the second highest cause of death overall, and the leading cause of premature death before the age of 65 years in 28 of the 53 European countries [1]. There is therefore now a clear demand for efficacious cancer therapies suitable for an ageing population.

For the last 30 years, hazardous drugs, such as antineoplastic chemotherapy agents, have commonly been used to treat cancer patients. The potential risks of these compounds do not only apply to the treated patients, but also to the pharmacists and other healthcare workers who need to handle them. These risks include:

- adverse reproductive outcomes such as miscarriages, birth defects, foetal losses, and infertility
- acute symptoms such as irritation, sore throat, cough, dizziness, headache, allergic reaction, diarrhoea, nausea, and vomiting.

Because of these known safety issues, guidelines for the safe handling of IV chemotherapy agents are now well established in both hospitals and ambulatory oncology clinics.

In recent times, however, a few important environmental changes have emerged. Firstly, the clinical and logistical responsibilities for handling cytotoxic agents have fallen increasingly on the pharmacist. Secondly, tumour therapy documentation, quality management, and interdisciplinary process standardisation have all gained importance. This has culminated in expanded therapy protocols and more stringent clinical treatment guidelines. Thirdly, as the number of oral cancer treatments has increased, greater emphasis has been placed on the prevention of non-adherence, errors of application, and interactions resulting from insufficient patient education.

As a result of these changes, adequate, quality-assured, multiprofessional care is now required for all oncology patients. Pharmacists must collaborate with all other relevant members of the healthcare team to ensure the delivery of the following goals:

1. On-site optimisation of oral chemotherapy and improvement of pharmaceutical care
2. Provision of cost-effective and reliable care through professional and timely collaborations between local physicians, pharmacists, and other healthcare professionals
3. Recognition and successful management of chemotherapy-related issues
4. Enhancement of patient quality of life through a coordinated management of side effects and interactions during and after therapy
5. Provision of a new insight which contributes to health service research and encourages drug safety

Currently, quality control in the preparation of cytotoxic drugs, and the exact role of the pharmacist with regard to the handling and management of oral tumour therapies, is addressed in both European guidelines and directives, and individual national/regional guidance. Oral tumour drug handovers have traditionally been performed by trained hospital pharmacists, but in some countries, e.g. Germany, this responsibility also extends to community pharmacists. This poses a huge educational challenge, both in terms of teaching pharmacists how to handle cytotoxic drugs safely, and in explaining how best to communicate essential information to patients.

In June 2011, the ESOP Secretary, Professor Per Hartvig-Honoré, spread the Society's international 'Pharmacist Counselling Plan' message at the Open Forum of the European Partnership for Action Against Cancer (EPAAC) in Madrid, Spain. This plan, which has been supported by seven countries, clearly stipulates the future role that pharmacists will play in this complex setting. I am sure that every one of ESOP's 2,500 members will be relishing the challenge!

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Safe handling of oral chemotherapeutic agents: a European perspective

Klaus Meier, PharmD; Niesha Griffith, MS; Susan Goodin, PharmD; et al.

In a series of roundtable meetings, a team of pharmacists from North America and Europe reviewed existing guidelines and identified gaps in recommendations for handling of oral chemotherapeutic agents. The present article is a compilation of these gaps.

Introduction

Traditionally, chemotherapy has been administered by IV infusion in an oncology inpatient unit or clinic or a physician's office. Over the past decade, however, self-administration of oral chemotherapy has increased owing to the availability of novel therapeutic agents [1-3]. In contrast to administration in the institutional setting, where the prescribed medication, dose, regimen, and response to therapy are subject to several levels of assessment, patient or caregiver (defined as family members or friends who assist the patient) administration of oral chemotherapy is more likely to be susceptible to errors, non-adherence, and increased adverse events as a result of a lack of coordinated care.

Accidental exposure to oral chemotherapy can occur at various stages during the handling of these agents, i.e. transport, unpacking, storage, handling, administration, and disposal [4-6]. Thus, guidelines for safe and appropriate handling across the healthcare continuum are imperative. Some of the existing recommendations to ensure the safe handling of cytotoxic oral chemotherapy are listed in Table 1 [2, 4, 7-24]. However, the recommendations have not been universally accepted or incorporated into practice. Recent surveys of healthcare practitioners as well as patients found that the perception of oral chemotherapy being safer than intravenous chemotherapy was prevalent [25, 26]. In addition, a survey of pharmacy directors of National Cancer Institute-designated cancer centres published in 2007 identified gaps in pharmacy practices, safety assessments, and prescribing methods and demonstrated the need for safe practice guidelines [27].

During a review of existing guidelines, our international panel of pharmacists found that none of the guidelines addressed all areas the panel deemed critical for the safe handling of oral chemotherapeutic agents. In our original article [28], we outlined recommendations to address these critical areas that could serve as a starting point to build a framework for the safe storage, handling, administration, and disposal of oral chemotherapeutic agents for manufacturers and distributors, healthcare workers, and patients or their caregivers. Here within, these guidelines are reproduced with the addition of commentary that points out recommendations of particular importance to oncology practitioners in many European countries.

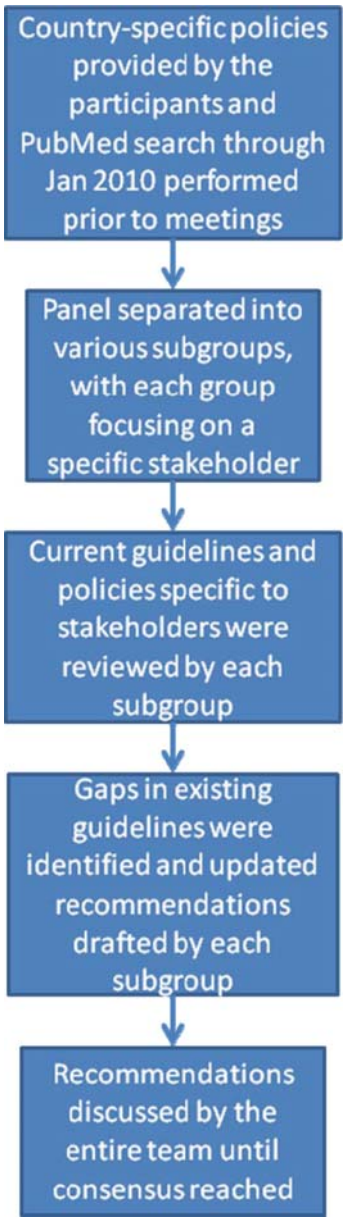
Methods

Details of the methods used to develop these recommendations are reported in our earlier article [28]. Briefly, an expert panel comprising pharmacists from Austria, Canada, France, Germany, Spain, UK, and the US, representing hospital, community, ambulatory care, and specialty pharmacy convened for a series of three roundtable meetings. Before the meetings, representatives from each country provided any current available national recommendations for handling oral chemotherapy, including guideline documents and institutional or country policies. In addition, a literature review was performed through PubMed

Table 1: Guidelines and policies for safe handling of oral chemotherapeutic agents

The US Department of Labor Occupational Safety and Health Administration technical manual [7]
Guidelines from the American Society of Health-System Pharmacists [12]
National Comprehensive Cancer Network (NCCN) Task Force Report on Oral Chemotherapy [2]
Recommendations from the National Institute for Occupational Safety and Health (NIOSH) [8]
American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards [19]
Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS) document (Canada) [4]
Guidelines from the Canadian Association of Pharmacy in Oncology [16]
The European Society of Oncology Pharmacy (ESOP) declaration [38]
National patient safety agency. Risks of incorrect dosing of oral anti-cancer medications. NPSA/2008/RRR001 [20]
The Merseyside & Cheshire Cancer Network guidance document (UK) [11]
The Society of Hospital Pharmacist of Australia Committee of Specialty Practice in Cancer Services. Standards of Practice for the Provision of Pharmaceutical Care of Patients Receiving Oral Chemotherapy for the Treatment of Cancer [22]
Guidelines for the Safe Prescribing, Dispensing and Administration of Cancer Chemotherapy; a consultative report prepared by Clinical Oncological Society of Australia, November 2008 [17]
The Grampians Integrated Cancer Service guidelines (Australia) [9]
The Management and Awareness of Risks of Cytotoxic Handling (MARCH) guidelines [24]
Relevant publications [10, 13-15, 18, 19, 21, 23]

Figure 1: Methodology involved in the development of the recommendations for safe handling



to search for relevant publications and existing guidelines through January 2010. All the guidelines reviewed at the meetings are listed in Table 1. In addition to existing guidelines, the panel also drew on best practices that were based on the professional experience of its members. A flow chart of the methodology is shown in Figure 1. The goal was to develop a framework of recommendations that can be included in guidelines specific to individual institutions and practices.

Recommendations for safe handling

A number of stakeholders are involved in handling oral chemotherapeutic agents at various stages. Recommendations for safe handling by these stakeholders are outlined in the following sections.

Manufacturers and distributors

There are well defined regulations for manufacturers and distributors to ensure safe transport and handling of chemotherapy drugs. Although the initial step for safe handling of oral chemotherapy agents begins with the manufacturer, recommendations for manufacturers and distributors are not included in current published safe handling guidelines, see Table 1, but the panel believes they play a pivotal role. Appropriate packaging could minimise the handling of chemotherapy by healthcare providers and patients, contributing to safer handling. This includes clear labelling on the outside of the package indicating that agent is cytotoxic. In addition, manufacturers should package only the amount of tablets or capsules needed for one cycle of therapy. Because new regimens are constantly developed and approved, another approach for manufacturers is to use unit-of-use packaging, thereby reducing the need for packaging based on a cycle of therapy. Each of these steps will ensure limited handling of these agents. Finally, manufacturers are encouraged to develop a liquid formulation or provide information on compounding a liquid formation of their product for use by children or in special circumstances such as patients with oral problems. Additional recommendations for manufacturers and distributors are listed in Table 2. Healthcare professionals are encouraged to reinforce the importance of these points to stakeholders and regulatory agencies whenever possible.

Healthcare providers

Healthcare providers have a major responsibility in ensuring safe handling of oral chemotherapeutic agents. Because of the significance of this responsibility, healthcare providers should be appropriately trained, ensure that their knowledge is current with developments in the field, and follow all applicable discipline-specific guidelines when handling oral chemotherapeutic agents.

Training and competencies

As recommended in most safe handling guidelines, healthcare professionals should attend multiprofessional orientation

Table 2: Recommendations for manufacturers and distributors

Packaging and segregation
Effective packaging and segregation techniques should be used to avoid contamination prior to distribution
Packaging should clearly state whether segregation techniques have been used so that individuals unpacking the medications can take additional precautions if necessary
Packaging material should be durable, able to contain any accidental leakage during handling and transport, and tamper-proof
Package label should indicate that the agent is cytotoxic, e.g. size-appropriate modifications of the European Society of Oncology Pharmacy yellow hand, the Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales 'C' symbol
Distributors should ensure that the labelling on the packaging is intact and that oral cytotoxic agents are stored and transported separately from non-cytotoxic agents
Minimising handling of oral chemotherapeutic agents
Manufacturers should provide the appropriate number of tablets or capsules per packing based on the amount needed for one cycle of therapy. If this approach is not an option, manufacturers should attempt to use unit packaging, i.e. individual packaging for tablets or capsules. Additionally, based on treatment protocols for various diseases being treated and new data, manufacturers should consider preparing additional dosage strengths as appropriate
Because many patients inherently, or as a result of their disease, have difficulty swallowing tablets or capsules, a liquid formulation, or information on how to compound a liquid formulation, should be provided by the manufacturer
Educational materials
Manufacturers should provide educational materials regarding safe handling to each stakeholder, including physicians, registered nurses, pharmacy personnel, patients, and caregivers
Manufacturers should update patient education materials as new information becomes available

programmes and routine training courses specific to their roles. They should also complete competencies associated with these training programmes, along with an accompanying assessment for licensing qualification if applicable. The training programmes should be approved by an oncology organisation or appropriate local organisations [29, 30]. In addition, within a healthcare institution, a primary educator should be established as a source of referral and continued education for training healthcare professionals on oral chemotherapy. This would ensure that patients receive consistent education, training, and monitoring across the multidisciplinary team [31, 32].

Healthcare workers should be trained and competent to treat individuals accidently exposed to chemotherapeutic agents and on the disposal of cytotoxic medications. All clinical staff who are likely to come in contact with oral chemotherapeutic agents or with waste from patients who have received these agents, e.g. clerks, hygiene workers, and sanitation workers should undergo appropriate training. The latter point of training non-healthcare professional staff was important to the panel because this recommendation is not included in any guidelines. With the changing paradigm of oral chemotherapy, these individuals should be appropriately trained as the traditional systems of handling chemotherapy, and those involved, are more diverse with oral chemotherapy. A list of training recommendations for healthcare providers is compiled in Table 3.

Storage and handling

Healthcare providers less than 18 years of age should not handle oral chemotherapeutic agents. When handling oral chemotherapeutic agents, healthcare providers must adhere to good practice as defined by local standard operating procedures and national guidelines. Key recommendations are outlined in Table 3. In many countries in Europe, oral chemotherapeutic agents are often available in unit packaging, reducing the need for handling by the pharmacist. Therefore, the recommendations regarding the handling of chemotherapeutic agents are applicable to those agents not available in unit packaging or when additional manipulation of the dosage form is required.

Handling of oral chemotherapy by pregnant staff initiated a broad discussion by the panel, and no consensus was reached regarding a recommendation. However, based on a 1992 directive of the Council of the European Communities, laws in a majority of European countries mandate that pregnant women should not work with cytotoxic agents [33].

Another issue for handling that generated a significant discussion was the cleaning of non-disposable surfaces exposed to chemotherapy drugs. Currently, there are limited options for cleaning of these surfaces, although, in some European countries, limited data support the use of cleaning agents that have been validated for the removal of cytotoxic agents [34]. The panel agreed further research is urgently needed to develop a valid, readily available, and affordable decontamination agent for use in the healthcare setting and the patient's home.

Patient counselling

Healthcare professionals should provide patients and caregivers with education and training to ensure their understanding of safe handling procedures as well as thorough knowledge of proper administration of all medications. Patient literature and other educational materials should be monitored and evaluated to ensure that current and accurate information is being delivered.

Patient consent for oral chemotherapy should be obtained. Patients should be consulted and assessed for their ability to take oral therapy and to comply with their treatment plan. Tools are available to assist with this evaluation [35]. Patients should also be advised on all matters related to safe handling.

All current medications should be reviewed with the patient or caregiver to identify potential medication interactions or interference with dietary requirements, and clear dosing instructions should be provided, including what to do when a dose is skipped or when vomiting of a dose (spillage) occurs. During renewal of prescriptions, any potential medication and food interactions must be reassessed and discussed with the patient or caregiver. The patient should be made aware of the required monitoring arrangements by being provided with access to the written protocol and treatment plan from the institution where the treatment was initiated. Patients who are pregnant or breastfeeding should be counselled on recommended medications and their risk–benefit profiles.

Patients and caregivers

Recommendations for patients and caregivers are included in some guidelines but are limited in details, so the panel focused on these responsibilities and created a summary of dos and don'ts for patients that could be put into practice and provided to all patients, see Table 4. Caregivers should understand all information given to patients, including the transport, storage, dispensing, and disposal requirements to ensure safe handling. They must work with the patient and healthcare providers to ensure appropriate dosing for patients in their care and report any treatment-related adverse effects. Caregivers who are pregnant, breast-feeding, or children should not handle any chemotherapy medications or waste products. Finally, to further ensure the safety of these individuals and others in the patient's home, guidelines from Australia and Canada as well as European Society of Oncology Pharmacy recommend one or more of the following: handle patient's clothes and bed linen with gloves and wash separately from other items; double flush the toilet after use, during treatment and four to seven days after discontinuing chemotherapy; and clean toilet surfaces after use by the patient [4, 9, 36]. These recommendations are supported by a recent publication involving cyclophosphamide exposure that showed significant contamination on and around the toilet and that the use of gloves reduced personal contamination from

Table 3: Recommendations for healthcare providers
Storage
Proper storage and handling of oral chemotherapeutic agents should be ensured by healthcare professionals in order to prevent accidental exposure and to ensure the integrity of these medications
In healthcare institutions and pharmacies, cytotoxic agents should be stored in a designated area per the manufacturer's instructions, and separate from non-cytotoxic agents.
Some agents are air-, moisture-, and/or light-sensitive; therefore, storage specifications should be followed
Handling
Correct use of personal protective clothing and equipment should be instituted to minimise exposure and health risks [5, 6, 12]
Oral chemotherapeutic agents should not be dispensed using automatic counting machines
Disposable gloves should be used for dispensing. Hands must be washed before and after glove application
Manipulations such as compounding, crushing, cutting, or splitting should be performed in a biological safety cabinet or isolators* and should involve the use of personal protective equipment, which should be disposable
Separate equipment should be used for cytotoxic and non-cytotoxic agents
The pharmacist (or other qualified professional) should attempt to limit additional handling of hazardous medications by other healthcare professionals and should provide oral chemotherapeutic agents in a ready-to-administer formulation†
Healthcare professionals who store and dispense oral chemotherapeutic agents must have a written emergency plan in the event of a spill or accidental exposure. It is recommended that annual spill simulation exercises be conducted
An updated list of hazardous medications should be readily accessible to all healthcare personnel involved in handling of oral chemotherapeutic agents
Disposal and cleaning of contaminated materials
All disposable protective clothing as well as any disposable materials used while handling oral chemotherapeutic agents should be disposed of as cytotoxic waste according to the local waste disposal regulatory guidelines
All non-disposable materials exposed to chemotherapeutic agents, including counting trays, tools, surfaces, etc. should be washed or decontaminated‡ thoroughly after use
Training and competencies for safe handling
Healthcare professionals should attend orientation programmes and routine training courses specific to their roles, and should complete competencies associated with these training programmes along with an accompanying assessment for licensing qualification if applicable [29, 30]
A primary educator within a healthcare institution should be established as a source of referral and continued education on oral chemotherapy for healthcare professionals, allowing for consistent education, training, and monitoring across the multidisciplinary team [31, 32]
Healthcare workers involved in the handling of oral chemotherapy should be trained and competent to treat individuals accidently exposed to chemotherapeutic agents and on the disposal of cytotoxic medications
All clinical staff who are likely to come in contact with oral chemotherapeutic agents or with waste from patients who have received these agents, e.g. clerks, hygiene workers, and sanitation workers should undergo appropriate training

*Because of the widespread use of isolators in many European countries, the table in the original article [28] has been updated with this information.
†As oral syringes are rarely prepared from powder forms of medications in European countries, the table in the original article [28] has been modified to reflect this practice.
‡In some European countries, limited data support the use of cleaning agents that are validated for the removal of cytotoxic agents [34].

changing bed linens from one- to six-fold [37]. Because drugs may be eliminated from the body as active or inactive metabolites in sweat, saliva, urine, or stool for five to seven half-lives, the panel agreed these recommendations were important and should be implemented.

Conclusion

In this article, we report on gaps in existing guidelines for the safe handling of oral chemotherapeutic agents and highlight any differences in North American and European perspectives. It is encouraging to note that, for the most part, there is considerable overlap in the standards for ensuring the safety of healthcare professionals and patients with regard to the handling of oral chemotherapeutic agents. The differences identified by us include the overwhelming use of unit packaging and regulations barring pregnant women from handling oral chemotherapeutic agents in a majority of European countries.

Although the limitations of our approach include informal methods of panel selection, the lack of a voting method for consensus agreement, and a non-systematic literature review, there are significant strengths to the recommendations. Firstly, our recommendations are relevant to multiple stakeholders, beginning with the manufacturer. In addition, although the panel was comprised solely of pharmacists, this group has significant experience with safe handling of hazardous agents coupled with managing oral agents for all disease types. On the basis of on our international experience and best practices, we compiled key recommendations to fill the gaps of existing guidelines. Therefore, this article, which provides an international perspective, is timely, and is ideally suited to be a framework for the development of safe handling guidelines specific to individual institutions and practices.

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Table 4: Specific recommendations for patients and their caregivers [39-42]	
Dos for oral chemotherapy	**Don'ts for oral chemotherapy**
On receiving your prescription, review the package label, specifically checking medication name and dosage [18]	Leave medication in open areas, near sources of water, direct sunlight, or where they can be accessed by children or pets
Ensure that you completely understand when and how to take the medication and ask questions if there is any confusion	Store medications in the areas where food or drinks are stored or consumed
Transport and store medicine as instructed and as outlined in the packaging label [18]	Crush, break, or chew tablets
Use gloves if possible and wash hands thoroughly before and after glove application* If gloves are not worn, tip tablets and capsules from their container/ blister pack directly into a disposable medicine cup	Double up on doses, unless instructed by a healthcare professional
Administer the medication as instructed	Share prescriptions or medication
Keep a journal of adverse effects. Make a list of adverse effects for whichever healthcare professional has to be contacted immediately	Assume that oral chemotherapy is safer than IV chemotherapy
Consider using adherence devices. Use separate devices for cytotoxic and non-cytotoxic agents	Skip doses unless instructed by your physician
Report any overdosing immediately	Discard medication down the toilet or in the garbage
Keep information ready for necessary action in the event of accidental exposure (including emesis and accidental ingestion) [14, 18]	
Return wet, damaged, unused, discontinued, or expired medications to the pharmacist or hospital for disposal [18]	
Report all medications (prescription and non-prescription as well as complementary and alternative medicines) and any specific dietary requirements to the healthcare provider/prescriber at the time of assessment and consultation. Inform other healthcare professionals that you are on oral chemotherapy, e.g. surgeons and dentists	
Minimise the number of individuals coming in contact with the cytotoxic medications [18]	
Wash the patient's clothes and bed linen separately from other items* [4, 9]	
Double flush the toilet after use during, and four to seven days after discontinuing oral chemotherapy [4, 9]	
*It is recommended that caregivers wear gloves at all times while handling oral chemotherapeutic agents as well as contaminated items in order to minimise risk of exposure.	

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Implementing quality in the preparation of cytotoxic drugs

The pharmacy department must ensure that the treatment the patient receives is safe, effective and timely. This can be achieved by maintaining quality standards.

Introduction

In order to preserve and enhance the ability of the pharmacy staff to meet the needs of the cancer patient, all quality standards must be agreed and set. These standards must also be constantly monitored and documented in order to be maintained. This short article summarises the key points that must be put in place to implement a quality system in the hospital pharmacy.

Jeff Koundakjian
BPharm, MRPharmS

Quality manual and policy

A complete quality manual must be accessible and a quality policy must be in place. A mission statement should also be prepared with a document stating the objectives of the facility.

Personnel

The pharmacy should have a documented organisational structure that clearly indicates the responsibilities and accountability of each member of staff. A register should be held of the people qualified to prescribe, dispense, release and collect the completed preparation. Each member of staff must have a regular evaluation and a tailored training programme relevant to their job description and an individual training record.

Staff records should be kept of individual personnel workload together with exposure to cytotoxic agents. Accidents and injuries at work should be recorded, as should any absences from work due to illness.

Capacity planning

There must be a document stating the current capacity and available measures for handling changes in workload. Arrangements must be in place for emergency dispensing and a detailed contingency plan must be available to cover any unforeseen suspension of service.

Documentation and standard operating procedures

An approved, comprehensive documentation system must be prepared and all documents must be clear, detailed and reviewed regularly at defined intervals. Standard Operating Procedures (SOPs) are required for LAFC/isolator usage, cleaning, decontamination, facilities, and equipment. Records must be retained for the original construction specifications and validation documents of equipment and facilities, and also for the operation, cleaning, maintenance and fault logs.

SOPs are also required for generic substitutions; additions and changes to the prescription form and its approval; prescription check and verification including any alteration; approval for the final check of finished products, completed prescriptions and their release.

Further required SOPs include worksheet preparation and check; assembly and check of raw materials and disposables; any transfer, labels and labelling, use of protective clothing; entering and leaving the clean room; the packaging and storage of finished products; delivery of the finished products; handling spillage and waste; the ordering, receipt, storage and shelf-life of starting materials; formulary and protocol compilation and clinical trials.

Records must be made for all adverse incidents and near misses, investigations and actions taken and of all complaints received, regardless of the source. A regular summary report of these should also be produced, including the investigations and actions taken.

Audits

Audits, both internal and external, must be undertaken on a regular basis to monitor implementation and compliance with the agreed standards. There should be a named, independent quality assurance person for both types of audit.

Observations made during the audits should be recorded, together with any recommendations for corrective measures, which must be reviewed at the next audit or, if serious, as soon as possible. The audit report should be submitted to the Director of Pharmacy and a timescale agreed to remedy any deficiencies. The final report should be submitted to the Chief Executive of the hospital or clinic.

This article is based on a presentation by the author at the 7th Symposium of the International Society of Oncology Pharmacy Practitioners (ISOPP) 2010 in Prague, Czech Republic.

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Further reading

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Systematic reviews of resection of metastases in metastatic colorectal cancer

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Abstract

Study objectives: Three systematic literature reviews in metastatic colorectal cancer (mCRC) were performed, one to assess initial resectability rates, one to assess resection rates after conversion therapy for initially unresectable metastases, and one to assess survival following post-conversion therapy resection. Conversion therapy consists of mainly systemic therapies that are used to shrink tumours sufficiently to allow resection in previously unresectable disease.

Materials and methods: Relevant articles were identified through three separate electronic searches of MEDLINE, MEDLINE In-Process, the Excerpta Medica Database (EMBASE) and the Cochrane Library, and through manual searches of the reference lists of identified articles. The MEDLINE and EMBASE searches were limited to articles published in English, whereas the Cochrane Library search had no language restrictions.

Results: Sixteen studies examined initial resectability, and reported definitions of resectability and resection rates. Resection rates varied greatly, ranging from 4–55%. Seventy-four clinical studies investigated resection after conversion therapy for initially unresectable metastases (liver, lung or mixed). Again, they reported a wide variation in resection rates, with overall resection rates ranging from 1–75% and complete resection rates (R0) from 0–39%. From the 29 studies reporting post-conversion therapy resection survival data, overall median survival ranged from 20–63 months and median progression-free survival from 13 to 20 months.

Conclusion: The findings from these systematic literature reviews suggest that mCRC resection data from different studies should be interpreted and compared with caution due to differences between studies in definitions of resectability, study designs, patient populations, the year when studies were conducted, and the country/centre where patients were treated.

There is a need for more data on conversion therapy, particularly using monoclonal antibodies, and for long-term survival post-conversion therapy resection. Pharmacy practice is encouraged to initiate or participate in retrospective or prospective research which examines conversion therapy in their institution.

Keywords: Conversion therapy, metastatic colorectal cancer, monoclonal antibodies, resection rates, survival, systematic review

Introduction

Colorectal cancer (CRC) is currently the third most common cancer worldwide [1]. Approximately 20–25% of patients with the disease already have metastases at the time of diagnosis [2], and about 50–60% of patients diagnosed with the disease will eventually develop metastases [3, 4]. The most common sites of metastases in metastatic CRC (mCRC) are the liver and the lung [5]. For most patients with mCRC, treatment is palliative rather than curative. The goals of systemic treatment in these patients are to prolong survival and to maintain quality of life for as long as possible [6].

However, 10–20% of patients with mCRC have metastases that are resectable, and may potentially be cured through surgical resection of the metastases [7]. An additional 15–20% of patients whose metastases are not initially resectable may be converted to a potentially curable state by additional therapy (mainly systemic therapy), known as 'conversion therapy', followed by surgical resection of the metastases [8]. Thus, the goal of conversion therapy is to shrink, i.e. downstage, the metastases so that surgical resection can be performed [6].

The current standard systemic therapies for mCRC are chemotherapies and the monoclonal antibodies (mAbs) bevacizumab, cetuximab and panitumumab. The most commonly used chemotherapy backbones are FOLFOX (leucovorin, 5FU and oxaliplatin) and FOLFIRI (leucovorin, 5FU and irinotecan). Bevacizumab, a mAb against vascular endothelial growth factor A (VEGF-A), was first approved as a treatment for mCRC in 2004, followed by cetuximab (also in 2004) and panitumumab (2006). Cetuximab and panitumumab both target the epidermal growth factor receptor (EGFR) and are effective only in wild-type *KRAS* mCRC. Panitumumab is the only approved fully human anti-EGFR monoclonal antibody, while cetuximab is a chimeric agent. Recent studies suggest that the addition of mAbs to chemotherapy regimens offers benefits in mCRC in terms of increased response rates and increased resection rates [9-17].

The objective of this study was to systematically review the literature to assess initial resection rates, and resection rates and survival post-conversion therapy in patients with mCRC. This systematic review was performed principally to understand the existing data to facilitate hypothesis generation for further work.

Materials and methods

Search strategy

Three separate electronic searches were performed, one to evaluate rates of initial resectability, i.e. no conversion therapy required; one to evaluate resection rates after conversion therapy for initially unresectable metastases; and one to evaluate

survival following post-conversion therapy resection. The databases searched were MEDLINE, MEDLINE In Process, the Excerpta Medica Database (EMBASE) and the Cochrane Library. In addition to the electronic searches, manual searching of reference lists was performed. Citations/abstracts of identified studies were reviewed and assessed for relevance by two independent analysts. Full paper copies of studies considered to be relevant were then reassessed for inclusion against the criteria outlined below. Disagreements between the two analysts were resolved by discussion until a consensus was reached. For each search, data from relevant publications were extracted into a data extraction table by one analyst according to a predefined set of parameters. The data table was then checked for accuracy and detail by a second independent analyst.

Inclusion and exclusion criteria

Inclusion criteria were: studies estimating the percentage of mCRC patients with initially resectable metastases (liver or lung); studies evaluating the proportion of mCRC patients with initially unresectable liver or lung metastases who were eligible for resection following conversion therapy; or studies evaluating the survival of mCRC patients after resection of liver or lung metastases following conversion therapy. For completeness of the systematic reviews, conversion therapy included not only systemic therapy but also hepatic arterial infusion (HAI) or mixed HAI/systemic therapy. The systemic therapies of interest were the mAbs bevacizumab, cetuximab and panitumumab (alone or in combination with chemotherapy) and the standard chemotherapy regimens FOLFOX, FOLFIRI and XELOX (oxaliplatin and the oral drug capecitabine).

Relevant studies were required to be observational, randomised or non-randomised, single or multicentre, retrospective or prospective, and phase II, III or IV in design. Meta-analyses, systematic reviews, case series, registries, and abstracts from meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology were also included.

Exclusion criteria were: studies of non-metastatic CRC; studies of the prevention or detection of CRC; studies of potential biomarkers in patient samples; *in vitro*, preclinical or phase I studies; and editorials, letters to the editor, case reports, commentaries, interview-based research, legal cases, newspaper articles or patient education leaflets.

The MEDLINE and EMBASE searches were limited to articles published in the English language, whereas the Cochrane Library search had no language restrictions. None of the searches were limited by date.

The aim of these systematic reviews was to be exhaustive. Thus, studies reporting relevant data for each review were included provided they did not fulfil any of the exclusion criteria. Included studies were not required to report relevant data as a primary or secondary endpoint, meaning that data could be reported as part of the study inclusion process or as patient characteristics.

Definitions

In this study, data on conversion and resection rates, and survival after post-conversion resection, were grouped according to the location of the downstaged metastases: liver, lung or mixed. Liver metastases were further subdivided as selected (metastases confined to the liver only) or non-selected (liver and extra-hepatic metastases). The mixed group included studies where the location of downstaged metastases was either not specified or mixed, i.e. the patient population included patients with liver only metastases, liver and extrahepatic metastases, and/or lung metastases only.

Data were also analysed according to the method of conversion therapy: systemic (including chemotherapy and mAb therapy), HAI, or mixed HAI/systemic therapy; and according to whether conversion therapy contained a mAb agent. The conversion rate was defined as the percentage of patients converted from having initially unresectable metastases to having resectable metastases. The resection rate after conversion therapy was defined as the proportion of patients who actually underwent attempted curative resection of metastases following conversion therapy.

Data analysis

Extracted data from relevant studies were summarised into a macro-enabled Excel spreadsheet (one for each search). No statistical tests were performed; thus, all findings are presented descriptively.

Results

Initial resectability

A total of 792 citations/abstracts were identified in the search for data on initially resectable metastases. Of these, 61 underwent full-paper review. After analysis of the full papers, 13 relevant studies remained. In addition, three studies were identified from manual searching, giving a total of 16 relevant studies. Of these, 15 reported data on initially resectable CRC liver metastases, see Table 1. These studies were published between 1978 and 2009. No systematic reviews or randomised, controlled trials (RCTs) were identified; all studies were either observational or a case series.

Proportion of patients with initially resectable metastases and resection rates

Two types of relevant data were identified in the literature: (1) data on the proportion of patients with metastases considered resectable (regardless of whether resection was then actually performed); and (2) data on the proportion of patients who actually underwent resection of metastases without receiving any conversion therapy. Ten out of 15 studies presented data on the proportion of patients with liver metastases that were considered initially resectable: this proportion ranged from 9.3–55%. All 15 studies reported data on the proportion of patients who actually underwent resection of metastases without receiving any conversion treatment: this proportion ranged from 4–55%, see Table 1.

Table 1: Resection rates for initially resectable liver metastases (no conversion therapy)

References	Definition of resectability	Definition of unresectability	Number of patients with liver metastases	Number of patients with initially resectable liver metastases (% of all liver metastases)	Number of patients who underwent resection of initially resectable liver metastases (% of all liver metastases)
Wanebo et al. 1978 [18]	NS	NS	217	NS	29 (13%)
Bismuth et al. 1996 [19]	No predefined criteria of resectability with regard to number or size of tumours, or to locoregional invasion of perihepatic structures, provided resection was complete and macroscopically curative	Large size, ill location, multinodularity, and extrahepatic disease	434	104 (24%)	104 (24%)
Isenberg et al. 1996 [20]	No extrahepatic progression, in good general condition, 1–4 liver metastases involving < 40% of liver parenchyma	NS	142	NS	17 (12%)
Harms et al. 1999 [21]	Complete resection of the primary cancer, absence of extrahepatic tumours, and technical ability to resect liver metastases completely	Tumour growth, number or distribution of metastases, and/or poor performance status	449	245 (55%)	245 (55%)
Wigmore et al. 1999 [22]	No evidence of extrahepatic dissemination, and metastases able to be safely resected with reasonable probability of clearing macroscopic disease	NS	230	94 (41%)	84 (37%)
Lambert et al. 2000 [23]	≤ 4 metastases in a distribution believed to be resectable with intent to cure	Extrahepatic disease	318	73 (23%)	49 (15%)
Rosen et al. 2000 [24]	NS	NS	96	NS	34 (35%)
Adam et al. 2001 [25]	NS	Large size, ill location, multinodularity, and extrahepatic disease	872	171 (20%)	171 (20%)
Heslin et al. 2001 [26]	Patients who are technically resectable and physically able to undergo the operation	NS	174	NS	52 (30%)
Moore et al. 2002 [27]	≤ 4 hepatic metastases, disease confined to one lobe of the liver and no extrahepatic disease	NS	194	52 (27%)	23 (12%)
Adam et al. 2004 [28]	NS	Not possible to perform a curative hepatectomy leaving at least 30% of nontumoural liver parenchyma, or the presence of concomitant extrahepatic disease	1439	335 (23%)	335 (23%)

(*Continued*)

Table 1: Resection rates for initially resectable liver metastases (no conversion therapy) (*Continued*)

References	Definition of resectability	Definition of unresectability	Number of patients with liver metastases	Number of patients with initially resectable liver metastases (% of all liver metastases)	Number of patients who underwent resection of initially resectable liver metastases (% of all liver metastases)
Sjovali et al. 2004 [29]	Patients < 80 years old without indications of extrahepatic disease, surviving > 30 days after diagnosis of hepatic metastases, < 5 hepatic metastases	NS	537	50 (9%)*	21 (4%)
Titu et al. 2006 [30]	NS	NS	37	NS	9 (24%)
Cheng et al. 2008 [31]	NS	Predicted residual functional liver remnant < 35% after 1 cm margin of resection, patient physically unfit for operation, evidence of extrahepatic disease not amenable to resection, more than liver-only metastasis (metastases to liver and other organs)	45	20 (44%)	17 (38%)
Xu et al. 2009 [32]	Liver metastasis focus ≤ 4 or liver metastasis focus > 4 but localised to semi-liver lobe, the remnant liver volume ≥ 30%, without other organ metastasis or peritoneum polar lymph node metastasis	NS	669	312 (47%)	253 (38%)

*Hypothetical number as all liver metastases patients potentially resectable according to imposed criteria; NS: not specified.

Only two studies reported data on the resection of initially resectable CRC lung metastases [24, 33]. Brister et al. [33] reported that 9% of patients had initially resectable lung metastases, and 8% of patients underwent actual resection of these metastases. Rosen et al. [24] reported that six patients (55% of included patients with lung metastases) underwent resection of lung metastases with no use of conversion therapy.

Definitions of resectability/unresectability

Of the 15 studies reporting relevant initial resectability data for liver metastases, 10 (67%) gave a definition of resectability. These definitions varied greatly between studies, see Table 1. Authors included the following criteria in these definitions: absence of extrahepatic tumours (6 studies); technical ability to resect the metastases (5 studies); ≤ 4 liver metastases (4 studies); patient in good general condition/physically able to undergo the operation (2 studies); complete resection of the primary cancer (1 study); metastases involving < 40% of the liver parenchyma (1 study); disease confined to one lobe of the liver (1 study); patients < 80 years of age and surviving > 30 days after the diagnosis of metastases (1 study); and > 4 liver metastases but localised to the semi-liver lobe and the remnant liver volume ≥ 30% (1 study).

In six studies (40%), a definition of unresectability of liver metastases was given, see Table 1. Criteria included in these definitions were: extrahepatic disease (6 studies); large size, ill location and multinodularity (3 studies); patient unfit for operation/poor performance status (2 studies); not possible to perform curative hepatectomy leaving at least 30% of non-tumoural liver parenchyma (1 study); and predicted residual functional liver remnant < 35% after resection (1 study).

No studies provided a definition of resectability for lung metastases, but one study [33] gave a definition of unresectability: disseminated malignancy, multiple lung metastases, recurrence at primary site, unresectable primary tumour, associated disease, or terminal state.

Conversion and resection of initially unresectable metastases

A total of 789 citations/abstracts were identified in the search for data on conversion therapy and resection rates after conversion therapy for initially unresectable metastases. Of these, 154 underwent full-paper review. After analysis of the full papers, 41 relevant studies remained. In addition, 34 studies were identified from manual searching, giving a total of 75 relevant studies. Of these, one was a systematic review and 16 were RCTs.

The included systematic review [34] evaluated irinotecan, oxaliplatin and raltitrexed in the treatment of advanced CRC. In this review, a total of 11 studies were identified that included conversion therapy data. Resection rates following conversion therapy ranged from 9–35% for irinotecan-based combination therapy and from 7–51% for oxaliplatin-based combination therapy.

Data on conversion rates and resection rates from the 74 clinical studies are summarised in Table 2. Not every study

Table 2: Summary of conversion and resection rates for initially unresectable metastases from 74 clinical studies with relevant data

Location of metastases	Type of conversion therapy	Conversion therapy subgroup	Number of relevant studies and date range	Conversion rates	Resection rates after conversion therapy (all resection)	Resection rates after conversion therapy (complete resection, R0)
Liver, (selected)	HAI	NA	9 studies[1] (1999–2009)	23–61%	4–47%	3–36%
	Systemic	Chemotherapy and/ or biologic therapy	19 studies[2] (1999–2010)	10–44%	10–75%	8–41%
		Including bevacizumab	1 study[3] (2009)	No data found	15%	12%
		Including cetuximab	2 studies[4] (2008, 2010)	No data found	75%*	30–38%
		Including panitumumab	No data found	No data found	No data found	No data found
	Mixed HAI/ systemic	NA	6 studies[5] (2002–2009)	No data found	10–57%	16–39%
Liver (non-selected)	HAI	NA	No data found	No data found	No data found	No data found
	Systemic	Chemotherapy and/ or biologic therapy	21 studies[6] (1996–2009)	6.5–43%	2–48%	2–30%
		Including bevacizumab	1 study[7] (2009)	No data found	8%	6%
		Including cetuximab	5 studies[8] (2007–2009)	7%	7–30%	5–30%
		Including panitumumab	No data found	No data found	No data found	No data found
	Mixed HAI/ systemic	NA	2 studies[9] (2007, 2009)	No data found	5%	0–21%
Mixed	HAI	NA	No data found	No data found	No data found	No data found
	Systemic	Chemotherapy and/ or biologic therapy	23 studies[10] (2000–2010)	17%	1–32%	2–25%
		Including bevacizumab	2 studies[11] (2008, 2010)	No data found	8–9%	No data found
		Including cetuximab	3 studies[12] (2007–2009)	No data found	23–27%	5–21%
		Including panitumumab	No data found	No data found	No data found	No data found
	Mixed HAI/ systemic	NA	No data found	No data found	No data found	No data found
Lung	All	NA	No data found	No data found	No data found	No data found

HAI: hepatic arterial infusion; NA: not applicable; *Only 15/20 patients evaluated.
[1][35–43], [2][15, 44–61], [3][15], [4][56, 59], [5][43, 62–66], [6][15, 16, 19, 25, 28, 67–82], [7][15], [8][16, 76–78, 80], [9][83, 84], [10][9, 13, 52, 54, 60, 80, 85–101], [11][13, 101], [12][9, 80, 100].

reported the three outcomes of conversion rate, resection rate and complete resection rate (R0). Among those that reported conversion rates, the rates ranged from 6.5–61%; for those reporting resection rates post-conversion therapy, the rates ranged from 1–75%; among studies reporting the rate of complete resection (R0), the rate ranged from 0–41%, see Table 2. No data on the use of conversion therapy for lung metastases were found.

Survival following post-conversion therapy resection

A total of 1,589 citations/abstracts were identified in the electronic search. Of these, 566 were considered to be possibly suitable for full-paper review. The 566 citations/abstracts were reassessed to ensure that they included conversion therapy and survival data, leaving 98 articles for full-paper review. After analysis of the full papers, 22 relevant studies remained. In addition, eight studies were identified from manual searching, giving a total of 30 relevant studies. Of these, one was a systematic review and three were RCTs.

The systematic review was identified in the search for conversion rate and resection rate data for initially unresectable metastases, see above [34]. Of the 11 studies identified in the systematic review by Hind et al. [34], only two studies provided survival data on post-conversion therapy resection: the 5-year overall survival (OS) rate was 5–26% and the 5-year disease-free survival rate was 3–11% with oxaliplatin-based combination therapy.

Twenty-nine of the 30 studies identified in the current review reported survival data following post-conversion therapy resection. These data are summarised in Table 3. Not every study reported all four outcomes of interest: OS, progression-free survival (PFS), 3-year survival rate, and 5-year survival rate. The median OS ranged from 20 to 63 months and median PFS from 13 to 20 months among studies reporting these outcomes. The 3-year survival rate ranged from 50–86% in studies reporting 3-year survival data and the 5-year survival rate ranged from 33–94% in studies reporting this outcome measure. No data for survival following post-conversion therapy resection of lung metastases were found, and only one study with survival data following conversion therapy containing a mAb was identified.

Discussion

In the current systematic review, resection rates for initially resectable metastases varied greatly between studies from 4–55%, along with a wide variation in the definitions of resectability between studies. Similarly, great variation was also observed in post-conversion therapy resection rates (range 1–75%), and in the proportion of patients that achieved complete resection (range 0–39%). After post-conversion therapy resection, overall median survival ranged from 20 to 63 months and median PFS ranged from 13 to 20 months. The majority of the studies that were identified focused on liver metastases, and only very limited data for lung metastases were found.

There are several possible reasons for the large variation in resection rates. First, as the results of this review showed, definitions of resectability/unresectability varied greatly between studies, not just for initially resectable metastases but also for post-conversion therapy resection. In some studies, definitions of resectability/unresectability were unclear or absent. Even today, resectability is still not well defined [108].

Second, surgeon opinion as to which liver metastases are resectable is evolving over time with advancing surgical techniques. Until recently, the classic contraindications for resection of mCRC liver metastases were four or more metastases, disease outside the liver, metastatic nodes in the liver pedicule, a resection margin of less than 1 cm, the presence of co-morbid disease, incomplete resection of the primary tumour, and the involvement of more than two sushepatic veins [108]. However, advances in surgery and systemic therapy have improved the feasibility of performing liver metastases resection, and these contraindications are now outdated.

Third, none of the studies identified examined resection rates as a primary or secondary endpoint. Thus, the data could be affected by uncontrolled bias. Additionally, study patient populations varied between studies. Patient age, gender and comorbidities are factors that are likely to influence the decision about whether or not to perform resection. In some studies, it was not clear whether the patient population with liver metastases was 'selected' (metastases confined to the liver) or 'unselected' (liver and extrahepatic metastases).

Fourth, resectability and thus resection rates are likely to depend on the centre where the patient is treated, as this can vary across countries, regions, centres, and even oncology surgeons, partly due to differing experience [48]. Finally, resection rates have been increasing since the year 2000 due to improved surgical interventions, and the introduction of new chemotherapeutic and biological agents [109, 110]. Indeed, the evolution in systemic therapies has resulted in increased objective response rates [108]. Thus, the year in which the study was conducted could also have an influence on resectability and resection rates.

A large proportion of the studies reporting conversion therapy data for initially unresectable liver metastases were retrieved by manual searching (34/75; 45%). Possible reasons for the manual identification of such a large proportion of relevant articles include the fact that the searching of electronic databases relies on the correct indexing of articles and the use of appropriate key words in the titles/abstracts of articles. Since resection rates were not a study endpoint, it is likely that relevant studies would not necessarily include appropriate search terms in the title or abstract and would therefore be less easily identifiable in an electronic database search.

Table 3: Survival following post-conversion therapy resection from 29 clinical studies with relevant data

Location of metastases	Type of conversion therapy	Conversion therapy sub-group	Number of relevant studies and date range	Overall median survival (months)	Median PFS (months)	3-year survival rate (%)	5-year survival rate (%)
Liver (selected)	HAI	NA	5 studies[1] (2000–2009)	63	No data found	56–86%	35–71%
	Systemic	Chemotherapy and/or biologic therapy	9 studies[2] (1999–2007)	39–60	14–17	67–73%	34–50%
		Including bevacizumab	None	No data found	No data found	No data found	No data found
		Including cetuximab	None	No data found	No data found	No data found	No data found
		Including panitumumab	None	No data found	No data found	No data found	No data found
	Mixed HAI/ systemic	NA	1 study[3] (2003)	No data found	20	65%	No data found
Liver (non-selected)	HAI	NA	None	No data found	No data found	No data found	No data found
	Systemic	Chemotherapy and/or biologic therapy	8 studies[4] (1996–2009)	20–41	13	50–63%	33–40%
		Including bevacizumab	None	No data found	No data found	No data found	No data found
		Including cetuximab	1 study[5] (2007)	20	13	No data found	No data found
		Including panitumumab	None	No data found	No data found	No data found	No data found
	Mixed HAI/ systemic	NA	2 studies[6] (2002, 2007)	No data found	No data found	No data found	39–94%
Mixed	HAI	NA	None	No data found	No data found	No data found	No data found
	Systemic	Chemotherapy and/or biologic therapy	4 studies[7] (2004–2006)	40–47	No data found	No data found	No data found
		Including bevacizumab	None	No data found	No data found	No data found	No data found
		Including cetuximab	None	No data found	No data found	No data found	No data found
		Including panitumumab	None	No data found	No data found	No data found	No data found
	Mixed HAI/ systemic	NA	None	No data found	No data found	No data found	No data found

HAI: hepatic arterial infusion; NA: not applicable; PFS: progression-free survival.
[1][36, 38, 39, 41, 42], [2][44, 45, 47, 48, 50, 51, 53, 102, 103], [3][63], [4][19, 25, 28, 67, 75, 77, 104, 105], [5][77], [6][106, 107], [7][90, 91, 93, 96].

The current review also found that survival following post-conversion therapy resection has not been well studied. In particular, long-term (over 5 years) survival data were lacking. This highlights the need for studies that could provide such data; for example, prospective interventional trials, observational studies or registries.

Conclusion

In these systematic reviews resection rates in patients with mCRC varied greatly between studies, mainly due to differences in the definitions of resectability, study designs, patient populations, the year when studies were conducted, and the

country/centre where patients were treated. As a consequence, it was difficult to compare resection rates between studies and between treatments identified in the literature.

There is a need for more data on conversion therapy, particularly using monoclonal antibodies, and for long-term survival post-conversion therapy resection. Pharmacy practice is encouraged to initiate or participate in retrospective or prospective research which examines conversion therapy in their institution.

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Conflict of interest

Dr Meredith Edwards and Ms Shkun Chadda are employees of PRMA Consulting and received research funding from Amgen Inc. Dr Zhongyun Zhao and Dr Beth Barber are employees and stockholders of Amgen Inc. Amgen Inc provides financial support to the study but the authors are responsible for study design, analysis and interpretation of data.

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An Italian model to evaluate appropriateness and effectiveness of drugs

The national and regional registries of drugs in Italy provide effective models to appraise drugs newly introduced to the market and determine reimbursement prices.

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The requirement for every new drug approval is the demonstration of net clinical benefit, but even randomised controlled clinical trials may fail to demonstrate relevance in modifying the natural history of a disease, and costs may be too high in relation to the benefits to the population that may be obtained.

The cost of bringing a new drug to the market from discovery to phase III clinical trials is estimated at Euros 0.5–1.1 billion and requires 8–10 years [1]. These high development costs are translated into increasing costs to patients receiving the new drugs (or society as a whole when this is charged to national health services). Recently, new models have been proposed to accelerate the registration and the availability to the market of a new drug [2].

The 'accelerated model' is more often implemented by the EMA or FDA for oncology drugs, but this fast-track authorisation requires post-marketing studies to verify both effectiveness and lack of toxicity in the general population. Furthermore, the national health services need tools to determine the reimbursement price for each drug. In the UK, the National Institute for Health and Clinical Excellence (NICE) systematically assesses drugs and health technologies, and usually suggests the reimbursement of the proposed drug or technology to the UK National Health Service. The NICE preferred method to assess the value of an intervention is the quality-adjusted life year [3].

In December 2005, the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) activated a web-based national registry of oncology drugs, the *Registro AIFA-onco* or RFOM (monitoraggio-farmaci.agenziafarmaco.it), as an appraisal of new drugs introduced into the Italian market.

The website has since been extended to drugs of different categories, e.g. orphan drugs, antidiabetic, anti-HIV, antipsoriatic, cardiovascular and ophthalmology drugs. Preliminary registration is required for the institution/department and the dispensing pharmacy, and then the physician is allowed to prescribe from a list of high-cost oncology drugs. Every prescriber has to enter information on:

- the patient's vital statistics, disease, drug schedule (first time)
- toxicity, variations in dosage, final outcome (follow-up).

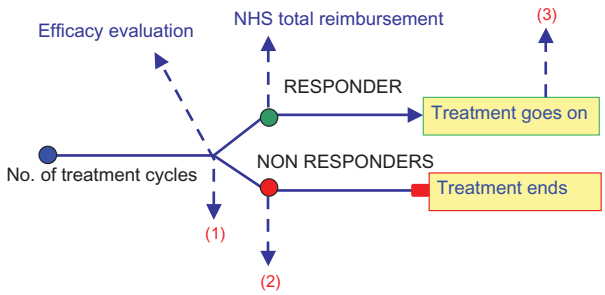
If all the elements match the required parameters, the prescription is allowed and the hospital pharmacist can dispense the drug. Standard reports are then made available on a local (hospital), regional and national basis. Table 1 shows the RFOM national statistics up to 28 September 2010.

Furthermore, the AIFA has recently adopted methods to appraise innovation and determine the reimbursement price of new drugs. In a document approved in July 2007, an AIFA working group suggested the following algorithm to establish drug innovation [4]:

Table 1: RFOM national statistics up to 28 September 2010

No. of enabled hospitals	788
No. of enabled hospitals with at least one patient registered	589
No. of enabled hospital departments	1,332
No. of enabled physicians	2,104
No. of enabled pharmacists	789
No. of registered patients	109,121
No. of patients eligible for treatment	103,085

Figure 1: Risk sharing or pay by result or by performance



(1) Cost-sharing: 50% discount to NHS on 'ex-factory' price for the first cycles of therapy, e.g. erlotinib, non-small cell lung cancer (NSCLC).
(2) Pay by result: 100% discount to NHS on 'ex-factory' price when treatment ends after one, e.g. lapatinib, metastatic breast cancer, or two, e.g. sorafenib, hepatocarcinoma, cycles.
(3) Combined methods: 50% discount to NHS on 'ex-factory'price for first cycles of therapy and 'capping'on payment after seven months of treatment, e.g. bevacizumab, colorectal, breast, NSCLC, renal cancers.

1. Definition in severity of disease
   a. treatment of severe disease
   b. treatment of risk factors in severe disease
   c. treatment of mild disease
2. Availability of treatments
   a. disease lacking a treatment
   b. treatment for resistant or non-responding patients
   c. disease with a known treatment
3. Extent of the effect
   a. clinical 'hard' endpoint
   b. partial benefit
   c. minor or temporary benefit

The industry then negotiates a price with AIFA, which can either accept, accept with restraint, or refuse to reimburse on the NHS.

As a conditional approval, the medicine can be prescribed within the NHS with fewer indications than those approved in the EMA SmPC. When the advantage is minor or not so clear, a 'risk sharing' or 'payment by results or by performance' method of pricing is adopted. This practice has permitted the combining of a high need for effective drugs with high reimbursement costs, offering rapid access to some medicines whose therapeutic and economic value is still uncertain. Figure 1 explains the most common features of the method.

The risk-sharing method requires an indicated use of the drug, certified through the RFOM. In recent years, an increasing number of Italian regions have set up reimbursement schemes under devolved financial arrangements. These practices allow clinical experience to be built while competent regional authorities fund high-cost medicines to the local health services. In the meantime, they provide access for patients to highly innovative treatments.

In January 2008, the Veneto region set up a web-based registry, to regulate the use of 11 high-cost IV oncology medicines that are specifically funded. This registry is stricter than AIFA-onco and requires specific protocols in a complete medical record. Tables 2 and 3 show the differences between the two registries.

The registeries can follow a huge cohort of oncology patients and enable inferences to be made of the effectiveness, toxicity and real costs of the treatments.

At the Venetian Oncology Institute (*Instituto Oncologico Veneto*), the hospital pharmacists deal with different information archives. They have integrated administrative archives and national/regional registers by record linkage and data mining to obtain information on length of treatment and, where available, outcome data.

Every patient is checked for length of treatment, and allocated in tables of frequency distribution and survival curves. The poor results obtained by some treatments (unpublished data and data in press) confirm the need for the risk-sharing option of AIFA and highlight the differences between real life treatment and clinical trials, where efficacy is obtained from data on selected patients.

Table 2: Comparison of the characteristics of the national (AIFA-onco) and the Veneto region (SIRFAC) registries

Item	National registry AIFA-onco	Veneto region registry SIRFAC
Start	December 2005	January 2008
Aims	Appropriateness – risk sharing	Appropriateness – funded access to high-cost oncology drugs (DGR 4051/2007)
Selection criteria	Innovative drugs	High-cost oncology drugs (IV)
Focus	20 drugs (to present day)	11 drugs in 156 protocols
Shared drugs	Bevacizumab, bortezomib, cetuximab, pemetrexed, rituximab	
Patients	All treated in Italy	Residents of the Veneto region
Patient outcome	Yes	Not yet
Report/ query	Standard reports	Not yet
Updating	Monthly (AIFA oncology board)	Annual (regional oncology committee and regional therapeutic committee)

Table 3: Comparison of oncology drugs recorded in the national (AIFA-onco) and the Veneto region (SIRFAC) registries

Item	National registry AIFA-onco	Veneto region registry SIRFAC
Monitored oncology drugs	bevacizumab, bortezomib, cetuximab (colorectal cancer), dasatinib, erlotinib, everolimus, gefitinib, ibritumomab, lapatinib, lenalidomide, nelarabine, nilotinib, panitumumab, pemetrexed, rituximab, sorafenib, sunitinib (renal cancer), temsirolimus, thalidomide, trabectedine	alemtuzumab, bevacizumab, bortezomib, cetuximab, docetaxel, irinotecan, oxaliplatin, paclitaxel, pemetrexed, rituximab, trastuzumab
Accrual closed (only data update)	carmustine wafer, trastuzumab (adj), oxaliplatin (adj), aprepitant, fulvestrant, temoporfin, palifermin	

Author and References

Author and References can be found on page 29.

Cytotoxics in the pipeline: carrier-mediated anticancer agents in development

Novel cancer pharmacotherapeutics are progressing speedily and are being implemented to solve several limitations of conventional chemotherapy. In this review, we will focus on the types and characteristics of carrier-mediated anticancer agents, how they are being used as drug delivery, and possible future advances.

Introduction

In 2015, cancer chemotherapy will commemorate its 70th anniversary since nitrogen mustard was introduced. Currently, nearly a hundred drugs have been registered worldwide for the treatment of cancer, but the rate of cytotoxics development has been held back due to the increasing cost burden of conducting clinical trials. Since a number of previously approved anticancer agents have gone off-patent, the carrier-mediated cytotoxic agents will likely be developed to improve their efficacy and safety profiles for forthcoming applications.

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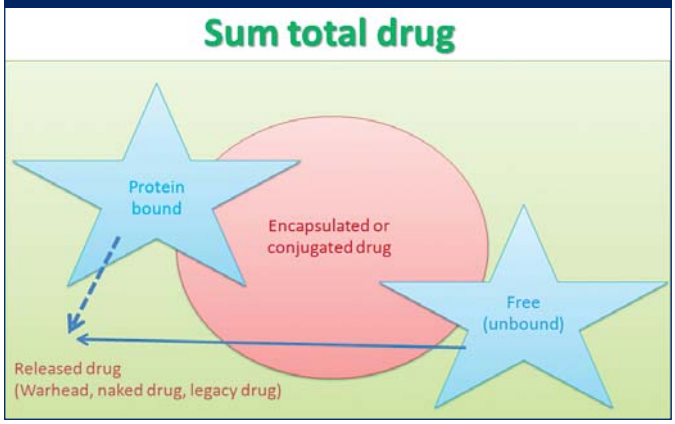
Types and characteristics of carrier-mediated anticancer agents

The major types of carrier-mediated anticancer agents are nanoparticles, nanosomes, and conjugated agents consisting of polymer-linked and pegylated agents [1-4]. Nanoparticles are submicron-sized particles (3–200 nm), or systems that can be prepared using a range of substances including polymers (polymeric nanoparticles, micelles, or dendrimers), lipids (liposomes), viruses (viral nanoparticles), and organometallic compounds [5]. The size of nanoparticles used in a drug delivery system should be bulky enough to prevent their rapid leakage into blood capillaries but compact enough to escape capture by macrophages located in the reticulo-endothelial system (RES), such as the liver and spleen [6-8].

The nomenclature used to describe the pharmacokinetic disposition of carrier-mediated drugs is encapsulated or conjugated, released, and sum total (encapsulated or conjugated drug plus released drug) [9]. The released drug has also been called the legacy drug, regular drug, or warhead consisting of a drug that is both protein bound and unbound, see Figure 1.

Figure 1: Nomenclature of carrier-mediated anticancer agents



The drug that remains encapsulated in or linked to the carrier, e.g. nanoparticle, is an inactive prodrug, and must be released from the carrier to be active.

How carrier-mediated anticancer agents work

Ideally, for anticancer agents to be effective in cancer treatment, they should be able to reach the preferred tumour tissues through the penetration of barriers in the human body with negligible loss of their quantity or activity in the blood circulation. Secondly, after reaching the tumour tissue, drugs should have the capability to selectively destroy tumour cells without affecting normal cells via a controlled release system of the active drug.

Conventional cytotoxic drugs are typically trapped in the circulation by the RES. In contrast, the carrier-mediated anticancer agents meet the size and surface characteristic requirements described above for escaping RES capture and have the ability to circulate for longer periods in the bloodstream with a greater chance of getting to the desired tumour tissues [10]. These features are described as the enhanced permeability and retention effect. This effect constitutes an important mechanism by which macromolecules, including carrier-mediated anticancer agents with a molecular weight > 50 kDa and size ≤ 100 nm, can selectively build up in the tumour interstitial tissue [10]. Consequently, the primary sites of accumulation are the targeted tumour leading to a better therapeutic index and with the potential to overcome resistance associated with the regular anticancer agent.

How to improve carrier-mediated anticancer agents functionality

Currently, pegylated STEALTH liposomal doxorubicin and paclitaxel albumin-bound particles are the only two members of this relatively new class of agents approved for the treatment of cancer in the US [11-12].

Paclitaxel albumin-bound system (Abraxane) uses a nanoparticulate shell constructed from albumin [12]. A major advantage of nanoshells is that they can be targeted to specific cell populations through conjugation with a monoclonal antibody. When the

nanoshell reaches the target site, it is ruptured using a low intensity light source such as a laser, and the therapeutic contents are released. This provides high target specificity with high potential for treatment of cancer with the chemotherapy agent paclitaxel, which normally has some possible life-threatening side effects due to a castor oil based solvent, cremophor.

In addition to the above products, nonpegylated liposomal formulations of doxorubicin and daunorubicin are also approved in Europe for the treatment of breast cancer and Kaposi's Sarcoma, respectively [13].

There are a number of nanosomal, nanoparticle, and conjugated anticancer agents currently in preclinical and clinical development. These include topoisomerase inhibitors (topotecan and irinotecan derivatives), anthracyclines, antimetabolites (pyrimidine, pyrimidine analogues, and antifolates), antimicrotubules (vinka alkaloids, and taxane derivatives), platinum analogues (cisplatin and oxaliplatin analogues) and interferon class agents.

Newer generations of carrier-mediated agents containing two anticancer agents within a single nanosome or nanoparticle and antibody-targeted nanosomes and nanoparticles that may improve selective cytotoxicity are in evaluation. Future multifunctional nanoparticles will be designed to have the ability to carry one or more therapeutic agents, or carry imaging signal amplification media, by way of co-encapsulated contrast agents. These nanoparticles will eventually be able to target tumour cells (active targeting moiety), visualise their location in the body (real-time *in vivo* imaging), destroying the cancer cells with no side effects by saving ordinary cells (active targeting and controlled drug release system), and monitor the treatment outcome in real time [14-15]. Nevertheless, future studies are still required in order to evaluate the mechanism of clearance of carrier-mediated agents and identify factors associated with the pharmacokinetic and pharmacodynamic variability of carrier agents in patients and specifically in tumours for more predictable responses.

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An Italian model to evaluate appropriateness and effectiveness of drugs
Author and References (please see article on pages 24–25)

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Erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia

Erythropoiesis-stimulating agent(ESA)-related safety concerns mean that clinicians must be vigilant when prescribing ESAs in cancer patients.

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ESA risks and benefits: evolving guidance

Anaemia is a common complication in oncology patients receiving myelosuppressive chemotherapy. As chemotherapy-induced anaemia (CIA) may affect patients symptomatically and prognostically, a number of treatment options are available, including red blood cell (RBC) transfusions and recombinant ESAs. ESAs work by increasing and maintaining haemoglobin (Hb) concentrations, improving quality of life, alleviating fatigue, and reducing the chronic need for RBC transfusions [1, 2].

Since 2007, published studies showing poor disease control and reduced overall survival have prompted a number of revisions to ESA product labels, see Table 1 [3]. Revisions have included the addition of a black box warning, and the implementation of a risk evaluation and mitigation strategy (REMS). Under REMS, patients are required to provide informed consent before receiving an ESA, and enrol in the Assisting Providers and Cancer Patients with Risk Information for Safe Use of ESA (APPRISE) Oncology Program [4]. Furthermore, the FDA has limited ESA use to non-curable patients receiving chemotherapy for palliative intent and advocates using the lowest possible doses, to help decrease the risk of venous thromboembolic events (VTEs). This follows a meta-analysis published in 2008 that suggested that ESA use in cancer patients was associated with an increased VTE risk [RR = 1.57, CI = 1.31–1.81]. However, it should be noted that the analysis did not investigate the correlation between VTE risk and higher Hb target levels [5].

The European Organization for Research and Treatment of Cancer (EORTC), the American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) have also recently updated their evidence-based guidelines on CIA management [6-8]. Currently, the EORTC recommends that in symptomatic patients and selected asymptomatic patients, ESAs should be initiated at Hb concentrations of 9–11 g/dL [6].

The ASH/ASCO and NCCN guidelines do not recommend ESA use in any patient not undergoing chemotherapy [7, 8].

NCCS ESA utilisation review

Our institution conducted a drug utilisation review of ESA

Table 1: Studies demonstrating adverse outcomes following ESA use

Study	Tumour type	n	Hb target (g/dL)	Achieved median Hb (g/dL)	Adverse outcome in ESA-containing arm
Chemotherapy					
BEST	Metastatic breast cancer	939	12–14	12.9	Decreased 12-month survival
2000-0161	Lymphoid malignancy	344	13–15 (M) 13–14 (F)	11.0	Decreased overall survival
PREPARE	Early breast cancer	733	12.5–13	13.2	Decreased 3-year relapse-free and overall survival
GOG 0191	Cervical cancer	114	12–14	12.7	Decreased 3-year PFS and overall survival and locoregional control
Radiotherapy alone					
ENHANCE	Head and neck cancer	351	> 15 (M) > 14 (F)	14.4	Decreased 5-year locoregional PFS, locoregional progression and overall survival
DAHANCA	Head and neck cancer	522	14–15.5	n/a	Decreased locoregional disease control and overall survival
No chemotherapy or radiotherapy					
EPO-CAN-20	Non-small cell lung cancer	70	12–14	n/a	Decreased overall survival
2001-0103/ Amgen 103	Non-myeloid malignancy	989	12–13	10.6	Decreased overall survival

PFS: progression-free survival; ESA: erythropoiesis-stimulating agent.

usage at the National Cancer Centre Singapore (NCCS). This revealed that the recent safety advisories had triggered a change in ESA prescribing, namely that clinicians had become more cautious. We observed a lower mean Hb level (8.52 g/dL vs 8.98 g/dL) for ESA initiation and a higher frequency of dose adjustments for excessive responders. However, our findings also showed that serum iron index monitoring and the provision of oral iron supplementation were still somewhat lacking in our practice [9].

Conclusion

Although ESAs can effectively manage CIA, clinicians must exercise caution when prescribing them. Clinicians must also recognise their inherent risks, and follow the latest ESA-related guidance.

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NEWS FLASH

Germany tightens controls on pharmaceutical prices

The German government is contemplating pharmaceutical price control legislation as it battles soaring drug spending. On the one hand Germany is keen to promote the use of generic drugs and generic medicines have already achieved high penetration—75% by volume in 2009. This highlights opportunities for generic manufacturers in Europe's largest, albeit competitive, drug market.

On the other hand, the government is hoping to cut Euros 2 billion from the sum it currently spends on new drugs. If a new law extends the current system of value-based pricing, companies bringing new drugs to the market will have one year to negotiate prices with health insurers. If no final price agreement is made, the health ministry will set a maximum price and the drug will face a cost–benefit analysis conducted by Germany's Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG], Germany's NICE). This type of system will not automatically lead to lower prices, the government and originator companies may agree a higher price if it can be justified. But other governments are watching with interest. If the new law is successful in lowering prices, it may lead to similar legislation in other European countries.

The drug price reforms that have already been enacted will also make a 'severe' dent in the sector's revenues. The mandatory discount that drug firms must offer to state health insurers has risen from 6% to 16%, and a 3-year price freeze will last until the end of 2013.

source: www.gabionline.net

35th ESMO Congress report: recent advances in cancer treatment

In this report, the major results of the clinical studies presented during the 35th ESMO Congress, which was held on 8–12 October 2010 in Milan, Italy, are reviewed and analysed in terms of their implications for oncology practice.

Introduction

A record number of attendees (16,000) made the 35th ESMO Congress a resounding success, including over 13,000 oncologists and other healthcare professionals involved in cancer care, 380 media representatives and close to 400 cancer patients who participated in a dedicated seminar. All educational materials from the congress are available from www.esmo.org/education/abstracts -and-virtual-meetings.html

Svetlana Jezdic
MD

Randomised phase III practice-changing studies

Professor Johann de Bono, Institute for Cancer Research and Royal Marsden Hospital, Surrey, UK, presented results of the randomised double-blind placebo-controlled phase III study that compared abiraterone acetate (potent and selective inhibitor of *CYP17α-hydroxylase*) versus placebo in 1,195 patients with castration-resistant metastatic prostate cancer. This is the first clinical trial that prospectively studied hormonal therapy after docetaxel treatment and the first clinical trial in prostate cancer with prospective collection of circulating tumour cells. It is also the first trial that prospectively used the Prostate Cancer Clinical Trials Working Group criteria in the context of a randomised phase III trial. Overall survival data shows clear advantages in favour of abiraterone acetate compared to placebo (14.8 months vs 10.9 months) and the drug also significantly improved time to prostate-specific antigen (PSA) progression, radiographic progression-free survival (PFS), and PSA response rate. A decrease in circulating tumour cells matches with the overall survival data and side effects show almost no difference compared to placebo. Further follow-up on survival data is awaited as well as a report on the potential long-term side effects [1].

Treatment options for advanced neuroendocrine tumours (NETs) are limited. In 429 patients with progressing well or moderately differentiated advanced NETs and a history of carcinoid symptoms, everolimus, an oral inhibitor of mTOR pathway, was administered together with octreotide LAR, and compared to placebo plus octreotide LAR. The study was presented by Dr Marianne Pavel, Charité University Hospital, Berlin, Germany, who showed a 5.1-month clinically meaningful increase in median PFS for the everolimus combination compared to placebo plus octreotide LAR. This should be considered for changing the current practice, as the alternative treatment is octreotide or a very aggressive chemo-embolisation. Another clinically meaningful report on 410 patients with advanced low- or intermediate-grade pancreatic NETs showed a 65% reduction in the risk of progression and an increase from 4.6–11.0 months in median PFS when everolimus was combined with the best supportive care and compared to placebo plus best supportive care. This study was presented by Dr James Yao, Anderson Cancer Center, Houston, USA [2, 3].

Novel targeted agents and randomised trials

Dr David Spigel, Sarah Cannon Research Institute, Nashville, USA, reported results of a study that included 128 patients with advanced non-small cell lung carcinoma (NSCLC). Patients were randomly assigned to treatment with either erlotinib plus placebo or erlotinib plus novel agent MetMAb, a monoclonal antibody that binds specifically to the MET receptor. This is the second trial in lung cancer where the targeting of MET receptors in combination with erlotinib suggests a better outcome. Immunohistochemically, the MET-positive population derived a benefit in PFS, and also an almost statistically relevant overall survival benefit. A note of caution is that these phase II results need to be validated in a phase III trial [4].

Dr Vincent Miller, Memorial Sloan-Kettering Cancer Center, New York, USA, reported that no established therapy exists for NSCLC patients who fail chemotherapy and erlotinib or gefitinib. Although the LUX-lung 1 study did not meet its primary

endpoint of extending overall survival, this does not diminish the potential value of afatinib (BIBW 2992); this new, irreversible inhibitor of EGFR/*HER1* and *HER2* induced objective regressions in heavily pre-treated NSCLC patients and led to a better PFS with improvements in some of cancer-related symptoms [5].

Dr Georgina Long, Melanoma Institute Australia and Westmead Hospital, Sydney, Australia, reported the results in a subgroup of 10 melanoma patients with previously untreated brain metastases from the international phase I/II trial with the selective oral inhibitor of V600 mutant *BRAF* kinase. The investigators described activity of this targeted agent in brain metastasis. All patients experienced control, and almost all experienced reductions in the overall size of their brain metastases. The overall reductions ranged from 20–100% of brain metastases that were > 3 mm before treatment. The ability to inhibit oncogenic *BRAF* is the most important development in the history of melanoma drug treatment [6].

New formulations of old drugs to innovate the therapeutic armoury

Examples of successes in this area are capecitabine and liposomal anthracyclines. Several new formulations of taxanes have been studied which aim to increase efficacy and/or decrease toxicity. EndoTAG-1 is an innovative formulation that tries to capitalise on the potential antiangiogenic proprieties of paclitaxel. In this new drug, paclitaxel is embedded in cationic liposomes and targets activated endothelial cells of tumour vessels. It is also innovative since it targets the environment and not the tumour cell itself. Results from the first randomised phase II study of EndoTAG-1 targeting tumour endothelial cells in advanced triple-negative breast cancer are somewhat disappointing since EndoTAG-1 alone does not seem to be a valid option, with PFS rate at week 16 inferior to paclitaxel alone, albeit with overlapping confidence intervals. Nevertheless, the apparent benefit of the combination arm merits further evaluation in a subsequent study. This study was presented by Dr Ahmed Awada of the Jules Bordet Institute, Brussels, Belgium [7].

Supportive care

Trastuzumab has been shown to improve disease-free and overall survival in patients with *HER2*-positive early-stage breast cancer. Standard adjuvant treatment by trastuzumab requires 52 weekly IV infusions over one year after chemotherapy and can result in discomfort, inconvenience and a significant time commitment for both healthcare providers and patients. Subcutaneous administration could significantly simplify treatment, shorten administration and improve patient experience.

Recombinant human hyaluronidase has been developed and approved to improve dispersion and absorption of co-administered drugs. It has been combined with trastuzumab to allow injection volumes ≥ 3 mL to be safely and comfortably administered SC. Dr Chris Wynne, Christchurch Clinical Studies Trust, Christchurch, New Zealand, presented results of a phase Ib study in which SC trastuzumab showed a tendency towards even fewer administration-related reactions than IV trastuzumab; furthermore, it achieved a serum exposure comparable to the approved IV formulation. The safety, tolerability and pharmacokinetic results of the study support the further testing of SC trastuzumab [8].

Most cancer patients suffer from chronic pain. Controlled studies with fentanyl pectin nasal spray demonstrate a rapid onset of effect and greater clinically meaningful pain relief compared to placebo and oral morphine. A new technology allows low-volume, fine-mist, and consistent particle-size delivery and therefore controlled dosing. The study was presented by Dr Luis Torres, Hospital Puerta del Mar, Cadiz, Spain, who reported that fentanyl pectin nasal spray can be easily titrated to an effective dose and could be used across a broad range of opioid-tolerant cancer patients. This is an interesting study but, as yet, it is too early for a change of current practice. More and more, nasal administration becomes a convenient and efficient route of administration and has potential for many other drugs [9].

In conclusion, the 35th ESMO Congress helped towards furthering our understanding of cancer biology, which should drive the treatment of the right patient, at the right time, with the right drug and dose.

The references referred to in the text are conference abstracts, which are available from: www.esmo.org/education/abstracts-and-virtual-meetings.html. The educational book containing summaries of all educational sessions held during the 2010 Milan Congress can also be downloaded for free via this link.

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ASCO 2011: setting new standards in malignant melanoma and myelofibrosis

The 2011 ASCO Annual Meeting, held on 3–7 June in Chicago, USA, included several landmark trials in malignant melanoma and myelofibrosis. This summary details some of the more interesting and relevant submissions.

Future cancer treatment strategies in daily practice

Gertrud Lenzen MD

Less is sometimes more

Oncologists regularly over-treat cancer patients. However, the application of modern molecular pathology techniques can help to reduce the use of ineffective therapies, saving cancer patients from undesired treatment effects, and saving the healthcare system unnecessary expense. Two important examples of this type of diagnostic technique are OncotypeDx in breast cancer and *KRAS* mutation testing in colorectal cancer.

Preventing human cancer

Some human cancer entities have specific aetiologies that can be interrupted. For example, the introduction of human papillomavirus vaccines has led to a reduction in the incidence of cervical dysplasias, and similarly, Goss PE, et al., Massachusetts General Hospital, Boston, USA, have demonstrated that exemestane offers a new option in breast cancer prevention [1].

The increasing importance of quality of life trials

Yoga improves sleep and reduces fatigue in post-chemotherapy patients. There are many specific quality of life improving techniques, often ignored by oncologists, that can improve cancer patients' well-being. Such supporting therapies should be made available as part of every primary standard treatment.

Trials that set new standards

Vemurafenib (PLX4032) improves survival in advanced malignant melanoma with V600E mutations in the *BRAF* gene

A phase III trial by Chapman P, et al., Memorial Sloan-Kettering Cancer Center, New York, USA, has shown that vemurafenib, which targets V600E mutations in the *BRAF* gene, improves overall survival in patients with advanced melanoma, when compared to standard DTIC (1,000 mg/m^2, IV, q3w). Vemurafenib is the first drug to achieve improved overall survival in this patient group, and the first drug to also improve progression-free survival. Vemurafenib can now be regarded as standard treatment for advanced melanoma in patients with this gene mutation.

Combining two distinctly acting oral targeted therapies shows significant anti-tumour activity in patients with advanced *BRAF* V600 mutation positive malignant melanoma

A phase I trial by Infante J, et al., Sarah Cannon Research Institute, Nashville, USA, has shown that a combination of two oral targeted therapies—the oral MEK inhibitor GSK212 and the oral *BRAF* inhibitor GSK436—is safe and has preliminary anti-tumour activity in patients with advanced malignant melanoma (*BRAF* V600-mutation-positive solid tumours). These results are important because they suggest promising synergistic anticancer activity for two distinctly acting oral targeted therapies.

First-line ipilimumab immunotherapy plus dacarbazine (DTIC) chemotherapy improves overall survival in metastatic melanoma

A phase III trial by Wolchok J, et al., Memorial Sloan Kettering Cancer Center, New York, USA, has found that first-line treatment with a combination of ipilimumab (10 mg/kg) and standard DTIC chemotherapy (850 mg/m^2) improves overall survival in patients with previously untreated metastatic melanoma. This is the first study to show that combining DTIC chemotherapy with ipilimumab is safe and effective in patients with advanced melanoma.

Palliative targeted therapy in JAK-positive primary myelofibrosis, post-polycythemia vera-myelofibrosis or post-essential thrombocythemia-myelofibrosis

A phase II trial by Harrison CN, et al., Guy's and St Thomas' NHS Foundation Trust, London, UK, has demonstrated that the JAK inhibitor, ruxolitinib, provides marked and sustained clinical benefit in spleen size and has an acceptable safety profile. These study data may result in a new standard of care for a large number of patients with myelofibrosis.

Trials that change or confirm standard treatment

Newly diagnosed diffuse large B-cell lymphoma: R-CHOP 14 is not superior to standard R-CHOP 21

Data from a randomised phase III trial by Cunningham D, et al., The Royal Marsden Hospital, London, UK, have indicated that cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab administered every 14 days (R-CHOP14) does not improve overall survival or progression-free survival in patients with newly diagnosed diffuse large B-cell non-Hodgkin's lymphoma, when compared with standard 21-day R-CHOP21 treatment. Patient status at 39 months, as measured by death, survival without progression, survival with progression or relapse, death with documented progression, and progression or relapse followed by death, was virtually identical for the two cohorts.

Standard first-line therapy of patients with chronic lymphocytic leukaemia (CLL)

Early-stage (Binet A and B, Rai 0-II) CLL patients who are asymptomatic do not usually require therapy. However, in patients with advanced (Binet C, Rai III-IV) or active symptomatic disease,

treatment should be initiated. For patients in good clinical condition, e.g. with a normal creatinine clearance and a low cumulative illness rating score, fludarabine plus cyclophosphamide and rituximab is the standard first-line therapy [2]. Chlorambucil remains a valid first-line treatment option for patients with relevant comorbidities. Patients with poor prognosis (del 17p and p53 mutation) should be considered for cytoreductive therapy and allogeneic stem cell transplantation following first remission.

Adjuvant treatment of operable gastrointestinal stromal tumours with a high risk of recurrence

A phase III trial by Joensuu H, et al., Helsinki University Central Hospital, Finland, showed that when compared with 1-year therapy, 3-year imatinib therapy (400 mg/day orally), administered following complete resection of a gastrointestinal stromal tumour (GIST), improved overall survival and recurrence-free survival in high-risk patients. This finding could lead to 3-year imatinib treatment becoming the new standard of adjuvant therapy in patients with resected high-risk tumours.

Maintenance therapy for advanced non-squamous non-small-cell lung cancer (NSCLC)

A phase III trial by Paz-Ares L, et al., Seville University Hospital, Spain, has shown that continuation maintenance therapy with pemetrexed (500 mg/m^2 on day 1 of a 21-day cycle) after a 4-cycle induction with pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2 on day 1 of a 21-day cycle) improves progression-free survival in patients with non-squamous NSCLC. This is the first large trial to demonstrate that longer-term maintenance therapy that includes a drug that has been administered during induction can increase progression-free survival in advanced NSCLC. This study may have uncovered a new treatment option following first-line therapy.

Preoperative chemoradiotherapy and postoperative chemotherapy for locally advanced rectal cancer

A phase III trial by Roedel C, et al., University Hospital of Frankfurt, Germany, has demonstrated that the inclusion of oxaliplatin to 5-FU-based chemoradiotherapy is well tolerated and associated with increased pCR-rates, when compared with 5-FU-chemoradiotherapy alone.

Prophylactic cranial irradiation in small-cell lung cancer

Schild SE, et al., Mayo Clinic, Scottsdale, USA, have performed a pooled analysis involving 739 patients with small-cell lung cancer (stable disease or better following chemotherapy +/- thoracic radiotherapy). The aim of the analysis was to determine whether the subsequent administration of prophylactic cranial irradiation (PCI) could improve survival. PCI was administered in 459 patients, at a total dose of either 30 Gy in 15 fractions or 25 Gy in 10 fractions. The remaining 280 patients received no cranial prophylaxis. The 1- and 3-year survival rates were 73% and 20% for the PCI-receiving patients, and 52% and 6% for the non-PCI patients ($p < 0.0001$). However, PCI did evoke an increase in adverse events including alopecia, anaemia, and lethargy. The investigators concluded that patients with either limited or extensive disease could benefit from PCI, unless they have progressive disease after primary therapy.

Dose-dense adjuvant temozolomid in newly diagnosed glioblastoma

A phase III trial by Gilbert MR, et al., MD Anderson Cancer Center, Houston, USA, has compared radiotherapy + concomitant standard adjuvant temozolomid (TMZ) with radiotherapy + dose-dense TMZ (ddTMZ), in 833 patients with newly diagnosed glioblastoma (GBM). The standard TMZ regime comprised 150–200 mg/m^2 for 5 days once a month and the dose-dense regimen was 75–100 mg/m^2 for 21 days of each 4-week period for a duration of 6–12 cycles. No differences in median overall survival or median progression-free survival were observed between groups, but increased overall survival was observed in patients with O6-methylguanine-methyltransferase promoter (MGMT) methylations. The authors concluded that MGMT methylation status was an important determinant of treatment response in patients with GBM.

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2011 EPAAC Open Forum

Professor Per Hartvig-Honoré, PharmD, PhD

The latest EPAAC Forum in Madrid, Spain, focused on cancer prevention and screening, and called for more uniform standards of cancer care across Europe.

The European Partnership for Action Against Cancer (EPAAC) was launched in 2009, following the publication of a European Commission report titled *Communication on Action Against Cancer: European Partnership*.

The aim of the Partnership initiative is to conjoin the efforts of different stakeholders to prevent and control cancer. In its initial phase, until early 2014, the work of the Partnership will be driven via a Joint Action (co-financed by the EU Health Programme). The National Institute of Public Health in Slovenia has assumed the role of leader of the EPAAC Joint Action, which encompasses 38 European associated partners and over 90 collaborating partners.

On 14–15 June 2011, the first of three EPAAC Open Forums was held in Madrid, Spain. The Forum's remit was to present the latest EPAAC working initiatives, the first of which focuses on cancer prevention. The highest risks for cancer, such as smoking, obesity, low physical activity, lower alcohol consumption, avoiding sun exposure, and avoiding cancerogenic substances, are well established. Nevertheless, 'we do not do what we know we should do', i.e. although these risk factors are obvious, there is only a very slow increase in adherence with regards to risk factor avoidance. EPAAC has developed excellent educational campaigns for a variety of cancers, and each May, it runs a dedicated *European Week Against Cancer*. This encompasses media advertisements, information leaflets, and campaign caps, all of which have helped to spread the word about the dangers of cancer to the general public. However, rather than resting on its laurels, additional campaign events and educational literature are expected in future years.

Another EPAAC initiative focuses on cancer screening. EPAAC has devised an initiative to develop specific screening tests, create a process of qualification and validation, and satisfy uptake of current and future guidelines to facilitate wider use. Standard tests have already been developed for breast, cervical, and colon cancers, but the initiative is also now seeking to incorporate Hepatitis B vaccination. There are various cancer registers in Europe, and the type of information they contain often differs. This makes it difficult to make valid comparisons. There is therefore a clear need both to better utilise existing registers, and compile new, more efficient and uniform registers which can increase our current knowledge. It is well known that cancer prevalence and disease outcomes vary widely across Europe, not least because of the diverse management and governance infrastructures. New studies now show that even in countries with restricted economies, the implementation of standards and good adherence can decrease mortality dramatically. Moreover, these results are only marginally less successful than those seen in countries with healthy economies.

Cancer care initiatives are currently fragmented across Europe. Many countries have their own treatment standards, with national practices often producing significantly different results from larger international trials. Research also tends to be fragmented. Research funding in the smaller countries is often restricted to that country alone, meaning that some research is duplicated, that the trials do not have sufficient patient numbers, and that the quality of the trials is often lacking. On a pan-European level, there are a number of eminent stakeholders such as patient organisations and industry representatives that would like to support and foster this research. The coordination of this support is currently lacking however. There are also important areas in cancer care that are often overlooked, including psychosocial care, pain control, management of vomiting and fatigue, nutritional support, and rare-cancer care. These important issues are also a focus for EPAAC.

The take-home message from the Open Forum was that despite us knowing a great deal about cancer care, best practice is often not delivered. Best practice implementation is often time-consuming, is rarely adhered to, and not extensively practised. During a poster presentation at the Forum, ESOP stated that it would very much like to become an active partner in this fight against cancer, and that in keeping with extensive and increasing evidence, any such initiatives required a multi-disciplinary professional approach.


EUROPEAN SOCIETY OF ONCOLOGY PHARMACY

The European Society of Oncology Pharmacy, founded in 2000 in Prague, is the largest organization of oncology pharmacists in the world with 2400 members.

ESOP

Pharmacist Counselling Plan

Aim and Objectives

ESOP supports optimal treatment for cancer patients with objectives to develop and promote clinical and oncology pharmacy practice through: 1. Education and training, 2. Safe handling and administration of drugs, 3. Quality management, 4. Research and development and 5. Pharmaceutical care. ESOP publishes its recommendations in the 4th edition of QuapoS (Quality Standard for the Oncology Pharmacy Service)[1]. Pharmaceutical counselling is described below as an example of these guidelines.

Pharmaceutical counselling

The oncology unit of the hospital pharmacy continually strives to implement pharmaceutical counselling and give advice to therapy. A direct contact with patients on cytotoxic drugs and infusions are demanded. Information are communicated directly to the patient or indirectly by producing and distributing written information and documentation. In addition the oncology pharmacist is a partner to physicians and nurses on advice for best drug treatment.

For implementation of counselling and advice a structured approach by the oncology pharmacist is required. Communication of therapy-related data from the physician is a cornerstone as well as direct patient contact for information on drug handling and administration when arriving home.

A counselling plan results from a systematic analysis of all drug-related problems (DRPs) for a patient. Using SOAP method design, the plan will contain:

Subjective: Complaints; Objective parameters (e.g. weight, blood count, creatinine & liver values), Assessment of problem(s) & identification of possible interventions and a Plan with therapy goals & control parameters.

Main advantages of such an approach are: (i) distinguish between medical & pharmaceutical DRPs, (ii) follow-up with measures & efficacy, (iii) continuous care within healthcare professionals, (iv) help the patient to be involved in his/her care (e.g. side effects' management).

Die Rolle der onkologischen Pharmazeuten ist es, für hochwertige hergestellte Arzneimittel und die Unterstützung für die Betreuung von Krebspatienten zu sorgen.

El farmacéutico especialista en oncología tiene como misión garantizar la calidad y seguridad de las preparaciones oncológicas así como proporcionar atención farmacéutica a los pacientes con cancer.

Apteekri roll on pakkuda vähihaigetele patsientidele nii kvaliteetselt valmistatud ravimeid kui ka kvaliteetset farmatseutilist hooli."

Le rôle des pharmaciens en oncologie est de fournir des préparations de médicaments de haute qualité et des soins pharmaceutiques aux patients atteints de cancer

Vloga onkoloških farmacevtov je skrb za zagotavljanje visoko kakovostnih zdravil in podporne terapije bolnikom z rakom.

De ziekenhuisapotheker is verantwoordelijk voor het op de juiste wijze voor toedienning gereed maken van de chemotherapie en het verstrekken van de gewenste informatie aan kankerpatiënten.