Editorial

Cover Story
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Meeting Report

Oncology Pharmacy Practice

Feature – Pharmacoeconomics

Guideline

Industry Science

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Working towards a better future for our patients

European oncology pharmacists from more than 24 countries have recognised the great opportunity of collaborating with all health-care workers in a multi-professional manner. They are teaching, learning, and expanding on the foundation of the quality standard, which has been discussed for more than 15 years in both national and European conferences to deepen our knowledge in order to deliver the best service for cancer patients.

Klaus Meier
Editor-in-Chief

EJOP

ECCO MEMBER

As we are not working for our own benefit, but for the optimal care of patients, we are happy to be collaborating with patient organisations that are an important pillar of communication for all the European Cancer Organisation (ECCO) member societies. The individual societies of ECCO had been on their own for a long time until ECCO was founded which unites everyone involved in oncology care in Europe.

A more fully developed exchange platform in educational activities currently under discussion with ECCO will certainly be of great benefit to everyone in the future. This will promote multidisciplinary collaboration and understanding, and enhance multilateral interaction in this field.

Since 2007, ESOP has already started to implement a Masterclass for quality in oncology pharmacy, which is an annual training opportunity for oncology pharmacists to learn the highest standards of quality practice. This expands the education from basic pharmaceutical topics to practical clinical works. This is the first step towards enhancing the common understanding in Europe concerning the needs and skills of European oncology pharmacists.

In this issue, we have articles touching on this area, such as, 'Drug interactions in oncology: the impact on cancer care', and 'Chemotherapy dosing in obese patients: the real evidence'.

When we are providing medical care services to the patient based on our pharmaceutical knowledge we are also confronted with demands that are often based on the given conditions.

The request to provide both the quickest and best service to the patient creates the discussion of dose banding or giving fixed doses to the cancer patients. We have a controversial article in this issue titled 'Fixed-dose versus patient-specific dosing of anticancer agents'. Thus, the article of 'Procedures (which) aid the oncology pharmacy in the preparation and supply of anticancer drugs' gives an insight into this discussion.

We must learn about many fields, including pharmacoeconomics and new drugs in development in order to treat patients with the best medication possible. Retel et al. gave us an insight into this topic in the article titled 'Establishing cost-effectiveness of genetic targeting of cancer therapies'. Pharmacists can add their opinions in the decision-making process in order to implement the most successful service possible with a pharmacoeconomic view.

Finally, I would like to inform you that in a few months we have the chance to be present once again at the 2011 European Multidisciplinary Cancer Congress, the ECCO 16, 23–27 September 2011 in Stockholm, Sweden, and to present our voice in the chorus of multi-professionalism.

EJOP – Call for papers

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

Paediatric oncology: a primer

Significant advances have been made in treating childhood cancers such that 80% of cases can now be cured. This has come at the cost of late treatment effects which impact the quality of life of survivors, and a realisation that there are sub-populations for whom cure remains elusive.

Introduction

There is no more devastating news that a parent can receive than to be told their child has cancer. The diagnosis affects not only the child but the entire family unit, disrupting family and work life and, potentially, creating anxiety in any siblings. A quarter of a century ago, most cancer diagnoses in children would have carried a poor prognosis; however, thanks to large multi-centre clinical trials, at present approximately 80% of children diagnosed with malignant disease can be cured.

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For a number of childhood/adolescent malignancies such as acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphomas and Wilms' tumour significant progress has been made, with cure rates to the order of 90% or better. Indeed, childhood ALL was the first malignancy in which clinical trials were run that did not have 'survival' as a primary endpoint.

Childhood neuroblastoma, the most common extracranial solid tumour in children, remains a challenge. While major advances in understanding the biology of this disease have allowed us to risk-stratify therapy for this malignancy, more than 50% of children still present with high-risk/metastatic disease at diagnosis. While improvements in treatment have resulted in gains in disease/event-free survival, overall survival has not improved significantly in the past 25 years and is currently around 30–35% [1-4]. The distribution of childhood malignancies is illustrated in Figure 1 and current overall survival rates are illustrated in Figure 2.

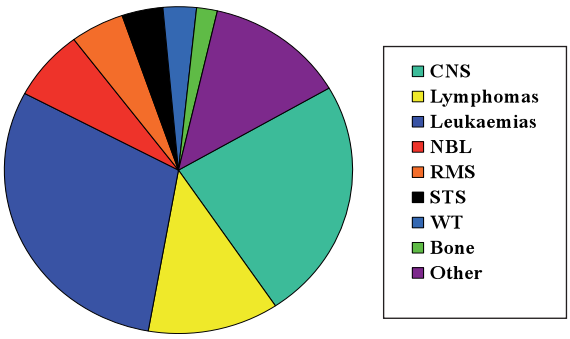
Childhood cancers are (fortunately) rare, accounting for only 2–3% of all malignant disease globally and thus answering the parents' most common question, 'Why did this happen to our child?' can be exceedingly difficult. A number of genetic syndromes such as Downs, Li-Fraumeni, Beckwith-Weidemann, and MEN-1 are associated with an increased risk of cancer. Several large epidemiological studies have identified circumstances associated with increased risk of malignancy in childhood. These include maternal X-ray exposure during the first trimester and maternal or paternal marijuana or cocaine use. Studies have also shown that very low birth weight infants have an increased risk of leukaemia, while those with a very high birth weight have an increased risk of soft tissue sarcomas. However, the overwhelming majority of cases are sporadic and no associated risk factor(s) or exposure can be identified [1].

Epidemiology and the challenge of 'numbers'

The rarity of childhood cancer creates a number of challenges for health professionals looking after these children and their families. Providing the best treatment for the child's particular malignancy is of the utmost importance. This is best accomplished in a centre with the appropriate multi-disciplinary health professional staff to diagnose accurately, stage, and provide the multi-modality treatment (surgery, chemotherapy, and radiation therapy) required for the child's disease. However, most specialised children's hospitals will still see too few children with cancer to answer the straightforward question, 'What is the best treatment for this malignancy?' [2].

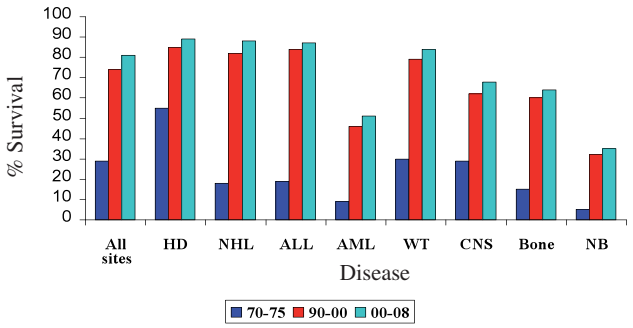
To address this challenge, a number of large multi-institutional cooperative clinical trial groups began forming in the 1970s. These have grown in number and size and now most children's

Figure 1: Distribution of childhood cancers



CNS: Brain tumours
NBL: Neuroblastoma
RMS: Rhabdomyosarcoma
STS: Soft tissue sarcoma
WT: Wilms' tumour
Bone: Bone tumours

Figure 2: Overall survival in childhood cancers



HD: Hodgkin's lymphoma
NHL: Non-Hodgkin's lymphoma
ALL: Acute lymphoblastic leukaemia
AML: Acute myelogenous leukaemia
WT: Wilms' tumour
CNS: Brain tumours
Bone : Bone tumours
NB : Neuroblastoma

hospitals which treat children with cancer will be members of, or affiliated to, at least one such clinical trial group and will be participating in the varied clinical trials and research agenda of their group. Indeed, it has been argued that having a child with cancer participate in a clinical trial of treatment, if one is available, constitutes standard treatment [3, 5]. These co-operative clinical trial groups have steadily advanced cure rates for the majority of childhood cancers and, with the exception of significant improvements in radiation technology in the past 15 years, this has not been accomplished (for the most part) with new drugs, but by using existing drugs better.

For pharmacists involved in the care of children with cancer on clinical trials, this brings the added dimension/responsibility of being familiar with relevant research methodologies and familiar with regulatory issues pertaining to investigational drugs under their jurisdiction. The specialised treatment of childhood cancer within centres of relevant expertise can also affect the family, as the specialised treatment centre may be very far (in some cases hundreds of kilometres) from home, and their particular regimen may require frequent visits to the centre for treatment, follow-up scans, or management of toxicities, e.g. mucositis or febrile neutropenia. This creates added personal and financial stress for the family in terms of costs of travelling, childcare for siblings at home and lost time from work for one or both parents [2, 6].

Clinical issues and special populations

While there is a significant amount of research into the oncogenesis and biology of paediatric cancers, the rarity of childhood cancer is a handicap in so far that it is not economically viable for the pharmaceutical industry to devote adequate resources to drug development for childhood cancers. This results in phase I and II studies of new agents for children lagging behind those of adult trials. Then, in some instances, agents may prove inefficacious or too toxic in the adult context, e.g. gemtuzumab, and be discontinued by the manufacturer before sufficient paediatric data has matured. Unlike a number of adult cancers, e.g. breast, colorectal, there are no mass screening programmes for childhood cancer. Because elevated urinary catecholamines (VMA, HVA) are highly sensitive and specific markers for childhood neuroblastoma, a mass screening programme of newborns was undertaken in Quebec, Canada. The hope was that early detection could catch the disease earlier while it was still curable. Unfortunately, the programme did not meet its objectives and did not change the survival of children with this disease. It did, however, detect a significant number of infants with elevated urinary catecholamines who were not ill but had large, still involuting adrenal glands; these glands usually shrink rapidly after birth [7]. The Children's Oncology Group observed these infants with large adrenal masses in a clinical trial.

In terms of providing pharmaceutical care for children with cancer, a number of important clinical characteristics distinguish them from their adult counterparts. As a rule, children will have overall better organ function (liver, renal, cardiac, pulmonary) which affects the clearance of drugs. Most tissues are more resilient to many of the on-going toxicities and side effects of chemotherapy, thus in general permitting higher doses of chemotherapeutic agents to be administered to children than adults. While this may result in better survival rates, it may also play a role in the development of troubling/chronic late effects of treatment in those children and adolescents that survive their cancer. The occurrence of late treatment effects has resulted in the development of childhood cancer-specific quality of life measures and highlighted the need to develop age-specific tools to assess toxicities of chemotherapy, especially for subjective or functional assessments such as neuropathies or musculoskeletal toxicities [6, 8].

In terms of specific toxicities of chemotherapy, neutropenia and febrile episodes occur with similar frequency to that of adults in children undergoing treatment for leukaemia or lymphoma and while the degree of neutropenia may be greater, the duration is often shorter. In contrast, children with solid tumours will have higher rates of febrile neutropenic (FN) episodes than adults with solid tumours. The spectrum of organisms seen in children with FN is similar to that in adults. However, due to having fewer co-morbid conditions, it has been possible to identify groups of children who are at low and very low risk of infection. The duration of antibiotic use can be reduced in these children, which has, in turn, improved rates of fungal infection and the need for antifungals [9, 10]. Neuropathies from agents such as Vinca alkaloids or etoposide can be more problematic in very young children than adolescents or adults; however these are reversible after treatment is complete and rarely result in permanent difficulties. While there is an association between thrombosis and cancer in adults this association is not as strong in children. The exception is in children undergoing treatment for ALL [3], especially during phases of treatment that include the use of L-asparaginase. Studies in this population report rates of thromboembolic events ranging from 1–35%. Tolerance of chemotherapy from the standpoint of nausea and vomiting is also generally better in children than adults, and is age dependent, with infants and toddlers experiencing less nausea than older children or adolescents receiving the same chemotherapeutic agent. The oncology pharmacist can play a vital role in educating children and families regarding the potential/expected side effects and toxicities of their particular treatment regimen and in monitoring the side effects and toxicities of chemotherapeutic agents as part of a multidisciplinary team [11].

Significant attention has recently been focused on adolescents and young adults with cancer. This group of patients has been significantly under-served by the medical community and has experienced the lowest rates of relative improvement in survival in the past 25 years. The reasons for this are multifactorial, but may be in part related to significantly lower rates of health insurance in some countries which may cause delays in diagnosis; unique psycho-social needs and very poor rates of participation in clinical trials [12, 13].

Summary

In summary, despite challenges stemming from the rarity of cancer in childhood, more than 80% of children diagnosed with cancer today can be cured. Current therapy strategies are now more focused on toxicity and mitigating the late/long-term effects of treatment and improving quality of life. The greatest challenge remains in making these cancer treatments available to the 85% of the world's children living in developing countries [14, 15].

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References

1. Surveillance, Epidemiology and End Results Database. Available from: http://seer. cancer. gov/csr/1975_2007/browse_csr.php?section=28&page=sect_28_table.11.html
2. Caldwell PHY, Murphy SB, Butow PN, et al. Clinical trials in children. Lancet. 2004;364(9436):803-11.
3. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Eng J Med. 2004;350(15):1535-48.
4. Maris JM, Hogarty MD, Bagatell R, et al. Neuroblastoma. Lancet. 2007;369(9579):2106-20.
5. Wagner HP, Dingeldein-Bettler I, Berchthold W, et al. Childhood NHL in Switzerland: incidence and survival of 120 study and 42 non-study patients. Med Pediatr Oncol. 1995;24(5):281-6.
6. Movsas B. Quality of life in oncology trials: a clinical guide. Semin Radiat Oncol. 2003;13(3):235-47.
7. Woods WG, Tuchman M, Robison LL, et al. A population based study of the usefulness of screening for neuroblastoma. Lancet. 1996;348:1682-7.
8. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adults survivors of childhood cancer. N Engl J Med. 2006; 355(15):1572-82.
9. Alexander SW, Wade KC, Hibberd PL, et al. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. J Pediatr Hematol Onc. 2002;24:38-42.
10. Wiernikowski JT, Barr RD, Pennie R. Prospective evaluation of a policy of early discontinuation of antibiotics and discharge from hospital in children with cancer who develop fever. J Oncol Pharm Pract. 2001;6:131-7.
11. Wiernikowski JT, Athale U. Thromboembolic complications in children with cancer. Thromb Res. 2006;118(1):137-52.
12. Bleyer A. Young adult oncology: the patients and their survival challenges. CA Cancer J Clin. 2007;57:242-55.
13. Bleyer WA, Tejeda H, Murphy SB, et al. National cancer clinical trials: children have equal access; adolescents do not. J Adolesc Health. 1997;21(6):366-73.
14. Ribeiro RC, Pui CH. Saving the Children-Improving Childhood Cancer Treatment in Developing Nations. N Eng J Med. 2005;352(21):2158-60.
15. Yaris N, Mandiracioglu A, Buyukpamukcu M. Childhood Cancer in Developing Countries. Pediatr Hematol Oncol. 2004;21(3):237-53.

Molecular imaging using PET/CT in oncology: current and future developments

Molecular oncologic imaging using PET/CT plays a significant role for accurate staging of tumours, monitoring response to therapy and in the follow-up after treatment by precisely characterising tumour metabolism, receptor status and functional properties of malignant cells.

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Grit Berger PharmD

Professor Richard P Baum, MD, PhD

Positron emission tomography (PET) is a non-invasive diagnostic modality to visualise biochemical processes and estimate metabolic changes in their temporal and/or spatial sequence. It involves the administration of biomolecules tagged with positron-emitting radionuclides and coincidence-detection of the resulting annihilation photons. Townsend et al. pioneered the concept of near-simultaneous imaging of molecular and anatomic information [1]. Positron emission tomography/computed tomography (PET/CT) combines the strengths of two well-established imaging modalities, CT for anatomy/morphology and PET for function/metabolism, into a single imaging device. The PET component has an extremely high sensitivity in the picomolar range with a detection limit of 10^5 to 10^6 malignant cells [2]. When combined with high resolution CT, PET achieves a high degree of accuracy through image fusion and also permits CT-based correction for attenuation. Thus, the clear advantages of PET/CT over PET alone are highly accurate shorter image acquisition times resulting in greater patient throughput and thus more efficient instrument utilisation, improved lesion localisation and identification, and more accurate tumour staging.

The Warburg effect, i.e. cancer cells which have abnormally accelerated rates of glycolysis in the presence of oxygen, was first observed more than 80 years ago [3]. This phenomenon of enhanced tumour cell metabolism enables the use of the glucose analogue 2-(^{18}F) fluoro-2-deoxy-D-glucose (FDG) for metabolic imaging of tumours. FDG is phosphorylated into FDG-6-phosphate (FDG-6P) by hexokinase. The substitution of fluorine for the 2-hydroxyl group of glucose blocks further metabolism of FDG, leaving FDG-6P trapped in the cell. The level of FDG uptake reflects the rate of FDG-6P trapping and hence the glucose metabolism.

FDG-PET/CT provides high diagnostic accuracy (having substantial impact on clinical management in up to 90% of all patients studied) as given by the following examples:

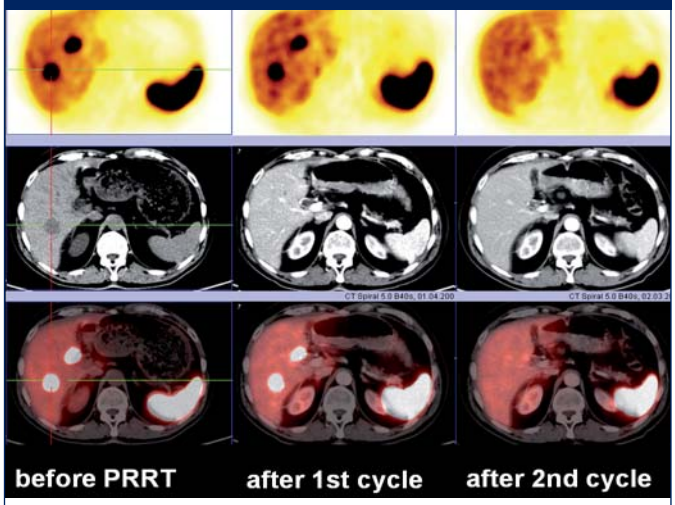
- **Lung cancer staging:** high sensitivity in detecting small-volume lymph node metastases and to rule out malignant involvement in enlarged, reactive lymph nodes and for detection of distant metastases [4].
- Diagnosis of **indeterminate solitary pulmonary nodules.**
- **Detection of recurrences** of lung, head and neck, colorectal, breast, ovarian, cervical and oropharyngeal cancer.
- **Staging of high grade lymphoma**, for the evaluation of residual masses after therapy of bulky **lymphoma** and for early evaluation of therapy response [5].
- In staging/restaging of high risk **melanoma, thyroid and esophageal cancer, and for detection of primary tumours in cancer of unknown primary syndrome** [6].

In addition, PET/CT allows monitoring tumour response early in the course of therapy, thereby individualising patient management [7]. Metabolic changes in tumours detected by PET usually precede anatomical alterations (tumour size) on CT. Hence, newer criteria for quantitative molecular imaging like PERCIST (PET response criteria in solid tumours) using PET/CT have been proposed [8]. Quantitative parameters to denote changes in subsequent PET/CT scans include the standardised uptake value (SUV) and molecular tumour volume. The results of molecular therapy response to peptide receptor radionuclide therapy with molecular tumour volume and quantification of the somatostatin receptor density were published recently, and the use of Molecular Tumour Index, which is a product of the Molecular Tumour diameter and the SUV, has also been described by our group [9]. PET/CT is a useful biomarker in order to monitor not only cytotoxic but predominantly cytostatic cancer therapies. As targeted therapies are expensive and cause considerable toxic adverse events, it is of high importance to identify potential responders early after starting therapy. Increasingly PET/CT (or PET and CT and magnetic resonance imaging scans fused by software as so-called anato-metabolic image fusion) is used for the molecular radiation treatment planning before radiotherapy of tumours (image-guided radiotherapy planning) [10].

[^{18}F]-Fluoride PET/CT is extremely valuable for assessment of skeletal metastases and yields superior resolution to bone scans acquired on a conventional gamma camera. In the last few years, new PET radiopharmaceuticals have widened the clinical usefulness of PET/CT, e.g. by using [^{18}F] Fluoroethylcholine for staging and detection of recurrences of prostate cancer and [^{18}F] Fluoroethyltyrosine for characteris-

ing low grade brain gliomas and in differentiating brain tumour recurrences from radionecrosis. The development of the ^{68}Germanium/^{68}Gallium generator has ensured high yields and safe and easy availability of the metallic positron emitter ^{68}Ga [11]. Somatostatin receptor PET/CT using ^{68}Ga-labelled somatostatin (SMS) analogues, e.g. ^{68}Ga DOTATOC, is now the new gold standard for imaging and quantitative evaluation of neuroendocrine tumours, especially before and after treatment, see Figure 1, with ^{90}Y and ^{177}Lu labelled SMS-targeting peptides [12]. A host of other ^{68}Ga labelled radiopharmaceuticals have the potential for routine application, e.g. ^{68}Ga-HSA microspheres (lung perfusion), ^{68}Ga-RGD (angiogenesis), ^{68}Ga-BPAMD (detection of osteoblastic metastases), etc. An exciting new development is the use of ^{68}Ga-labelled HER2 affibodies, e.g. ^{68}Ga-HER2 scan, for the *in vivo* characterisation of the herceptin receptor status of breast cancer patients—the first in-human study was performed by our group [13].

Figure 1: ^{68}Ga DOTATOC PET/CT imaging of neuroendocrine tumours



PRRT: peptide receptor radionuclide therapy

Nowadays, F-18 FDG is commercially available, and produced and distributed also by our centre. All other radiopharmaceuticals need to be produced in-house under good manufacturing practice conditions using a cyclotron (for production of the radiosotopes), a radiopharmaceutical laboratory with hot cells (lead-shielded fully automated modules for synthesis and special cells/modules for preparation of the radiotherapeutics, which emit beta irradiation), and a quality control laboratory ensuring a high pharmaceutical standard.

In summary, integrated PET/CT is able to pinpoint areas of sub-centimetre disease before biopsy or excision is performed and is now routinely performed early in the diagnostic workup of cancer patients. In the future, immuno-PET/CT and receptor-PET/CT will improve dosimetry of radionuclide therapy and by using reporter genes; gene-PET might enable us to monitor gene therapy. To ensure success of PET/CT in a clinical setting, the timely and accurate supply of the radiopharmaceuticals is essential. The logistic processes require an excellent cooperation between medical doctors, technicians, radiochemists and clinical pharmacists: the medical-pharmaceutical team.

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References

1. Townsend DW, Cherry SR. Combining anatomy and function: the path to true image fusion. Eur Radiol. 2001;11(10):1968-74.
2. Fischer BM, Olsen MW, Ley CD, et al. How few cancer cells can be detected by positron emission tomography? A frequent question addressed by an in vitro study. Eur J Nucl Med Mol Imaging. 2006;33(6):697-702.
3. Warburg O, Wind F, Negelein E. The metabolism of tumours. J Gen Physiol. 1927;8(6):519-30.
4. Hellwig D, Baum RP, Kirsch C. FDG-PET, PET/CT and conventional nuclear medicine procedures in the evaluation of lung cancer: a systematic review. Nuklearmedizin. 2009;48(2):59-69.
5. Hutchings M, Barrington SF. PET/CT for therapy response assessment in lymphoma. J Nucl Med. 2009;50(Suppl 1):21S-30S.
6. Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S, Baum RP. Detection of unknown primary neuroendocrine tumours (CUP-NET) using ^{68}Ga-DOTA-NOC receptor PET/CT. Eur J Nucl Med Mol Imaging. 2010;37:67-77.
7. Baum RP, Prasad V. Monitoring Treatment. In: Gary JR Cook et al. 4th ed. Clinical Nuclear Medicine. Hodder Arnold; 2006. p. 57-78.
8. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumours. J Nucl Med. 2009;50(Suppl 1):122S-50S.
9. Prasad V, Ambrosini V, Alavi A, Fanti S, Baum RP. PET/CT in Neuroendocrine Tumours: Evaluation of Receptor Status and Metabolism. PET Clin. 2008;3(3):355-79.
10. Zaidi H, Vees H, Wissmeyer M. Molecular PET/CT imaging-guided radiation therapy treatment planning. Acad Radiol. 2009;16(9):1108-33.
11. Zhernosekov KP, Filosofov DV, Baum RP, et al. Processing of generator-produced ^{68}Ga for medical application. J Nucl Med. 2007;48(10):1741-8.
12. Baum RP, Prasad V. PET and PET-CT imaging of neuroendocrine tumours. In: Wahl R, editor. Principles and practice of PET and PET/CT. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 411-37.
13. Baum RP, Prasad V, Müller D, et al. Molecular imaging of HER2-expressing malignant tumours in breast cancer patients using synthetic ^{111}In- or ^{68}Ga-labelled Affibody molecules. J Nucl Med. 2010;51:892-7.

Novel oral anticancer drugs: perspectives and limitations

Within the last decade, the development of novel, orally available anticancer drugs has made great progress, but this oral treatment requires the same amount of patient instruction as IV treatments.

Introduction

Surveys indicate that cancer patients may commonly prefer an oral route of drug administration in order to: (1) reduce the frequency of ambulatory visits related to parenteral drug application; (2) be more flexible in general, e.g. during employment or vacations; and (3) avoid the need for a peripheral or central venous access and potential related complications. In addition, daily oral drug intake may be associated with a more continuous drug exposure over time which may be beneficial compared to intermittent IV drug infusions, e.g. every 2–3 weeks, with respect to efficacious tumour control. Finally, oral drug treatment as an alternative route may allow better overall management of the increasing numbers of cancer patients in the near future [1].

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However, despite increasing enthusiasm, one must consider some potential risks which need to be discussed with the patient before oral drug regimens can be initiated, otherwise difficulties in adherence (compliance) resulting in potential over and underdosing may arise. These instructions should include: (1) the broad spectrum of side effects, e.g. capacitabine-associated grade 3–4 diarrhoea; (2) optimised supportive strategies to alleviate adverse events, e.g. thrombo-embolic prophylaxis during lenalidomide; and (3) potential food–drug and drug–drug interactions to avoid erratic drug levels in plasma, see Table 1. Additionally, changes in gastric pH may have an enormous impact on drug absorption, e.g. proton pump inhibitors and dasatinib [2-5].

These topics will be discussed in more detail in this article with the following examples: (1) pazopanib as a novel agent for oral treatment of advanced renal cell carcinoma (RCC); (2) a broader use of lapatinib in the near future based on an extended spectrum of approved indications; and (3) olaparib as an encouraging but not yet approved agent for the treatment of solid tumours.

Pazopanib

Pazopanib has recently been approved for the treatment of advanced RCC. Available data indicate that the drug may be as efficacious as sunitinib regarding first-line treatment of RCC, however, a direct head-to-head trial (COMPARZ) is ongoing, which may reveal potential differences between both drugs regarding efficacy or safety, see Table 2. With respect to potential food–drug interactions, it has been recommended to take pazopanib on an empty stomach to avoid more extensive intra-individual variability of drug levels in plasma, which is similar to sorafenib or lapatinib, but in contrast to sunitinib, see Table 1.

Whereas the use of sunitinib is associated with considerable side effects including neutropenia, dermatological reactions, fatigue, and more rarely thyroid dysfunction and stomatitis, pazopanib has been shown to be less toxic to the skin and bone marrow. However, the latter needs more intensified monitoring of liver function because an increase of ALT or AST has been reported to occur very frequently during continuous pazopanib administration, see Table 2 [6].

Lapatinib

Based on phase III study results (the EGF-30008 trial) which revealed a superior role of lapatinib in combination with letrozole compared to letrozole (monotherapy) in postmenopausal women with hormone-receptor positive metastatic breast cancer, the EMA has currently approved this combination regimen for patients in whom conventional chemotherapy is not indicated.

Whereas letrozole can be administered with or without food, lapatinib should be administered on an empty stom-

Table 1: Oral anticancer drugs: current recommendations for intake with or without food

Current recommendations	Oral anticancer drugs
Preferred intake on an empty stomach	Busulfan, Chorambucil, Erlotinib, Hydroxyurea, Lapatinib, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Nilotinib, Pazopanib, Sorafenib, Temozolomide, Thioguanine, UFT
Preferred intake with food	All-trans-retinoic acid (ATRA), Capecitabine, Idarubicin, Imatinib, Thalidomide (1 hour after a meal at bedtime), Treosulfan, Vinorelbine
Intake is feasible with food or on an empty stomach	Cyclophosphamide, Dasatinib, Etoposide (phosphate), Fludarabine, Gefitinib, Lenalidomide, Procarbazine, Sunitinib, Topotecan, Trofosfamide

Table 2: Pazopanib, sorafenib and sunitinib: comparative targeted therapy and side effects

Parameters	Pazopanib	Sorafenib	Sunitinib
Targeted enzymes	VEGFR 1,2,3 PDGFR-α,β FGFR-1,3, c-kit, IL-2 ltk, Lck, c-fms	VEGFR-1,2,3 PDGFR-β cRAF, B-RAF, FLT-3 RET	VEGFR-1,2,3 PDGFR-α,β, c-kit FLT-3 CSF-1R, RET
Skin rash	8 %	40 %	27 %
Hand-foot syndrome	6 %	30 %	21 %
Fatigue	19 %	37 %	58 %
Increase of AST, ALT	ca. 53 %	1–10 %	46–52 %

Based on reference [6]
VEGFR: vascular endothelial growth factor receptor; PDGFR-α and β,: platelet-derived growth factor receptor; FGFR: fibroblast growth factor receptor; c-kit: cytokine receptor; ltk: interleukin-2 receptor inducible T-cell kinase; Lck: leukocyte-specific protein tyrosine kinase; c-fms: transmembrane glycoprotein receptor tyrosine kinase; cRAF and B-RAF: cytosolic protein kinases; FLT-3: Fms-like tyrosine kinase-3; RET: the glial cell-line derived neurotrophic factor receptor; CSF-1R: colony stimulating factor receptor Type 1

ach, e.g. 60 minutes before a meal, based on the experience that absolute bioavailability is highly variable (factor up to 25-fold) when the drug is taken with fat-containing food. However, patients with highly increased plasma levels may develop more severe forms of diarrhoea or skin reactions [7].

Olaparib

It is highly likely that several novel oral anticancer drugs will be approved in the near future. Among those, the Poly ADP Ribose Polymerase (PARP) inhibitor olaparib has been suggested to be highly encouraging. Based on its ability to disturb intracellular DNA repair mechanisms in a selective manner in tumour cells whereas normal cells remain unaffected, the drug has been shown to be of considerable value to patients with advanced breast, ovarian or prostate cancer. The tolerability of olaparib appears to be good and fatigue, somnolence and thrombocytopenia are dose-limiting reactions at a maximum dose of 600 mg orally daily. Dosages of 200 mg two times a day are known to be particularly efficacious in carriers of the BRCA1 and BRCA2 mutation [8].

However, clinical pharmacists may be confronted with this novel agent before drug approval, e.g. in case of compassionate use. In those situations, more extensive information may not be available, in contrast to centres which are involved in clinical trials with this novel drug. However, drug information is necessary regarding clinical experience with respect to the extent of inter-individual drug variability following oral intake of recommended dosages; any impact of food or gastric pH on drug absorption; which metabolic pathways are involved during drug biotransformation, whether major metabolites may be as active as the parent compound, and whether concomitantly applied potent CYP3A inhibitors or inducers have a significant impact on drug levels in plasma.

Conclusion

Oral treatment with anticancer drugs requires the same extent of patient instruction as IV treatments. Oral, compared to IV, drug use is often associated with more variable levels in plasma based on the possible impact of various clinical pharmacokinetic parameters; as a consequence, appropriate patient instructions need to clarify potential drug–food and drug–drug interactions. Finally, patients should be guided regarding the most important drug-related adverse events with respect to frequency and severity in order to contact physicians in time and to adapt supportive strategies most appropriately.

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References

1. Banna GL, Collovà E, Gebbia V, et al. Anticancer oral therapy: emerging related issues. Cancer Treat Rev. 2010;36(8):595-605.
2. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents. Clin Pharmacokinet. 2004;43(15):1127-56.
3. Goodin S. Oral chemotherapeutic agents: understanding mechanisms of action and drug interactions. Am J Health Syst Pharm. 2007;64(9 Suppl 5):S15-24.
4. Koopman M, Antonini NF, Douma J, et al. Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer, an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) phase III study. Ann Oncol. 2006;17:1523-8.
5. Egorin MJ, Shah DD, Christner SM, et al. Effect of a proton pump inhibitor on the pharmacokinetics of imatinib. Br J Clin Pharmacol. 2009; 68(3):370-4.
6. LaPlant KD, Louzon PD. Pazopanib: An oral multitargeted tyrosin kinase inhibitor for use in renal cell carcinoma. Ann Pharmacother. 2010;44(6):1054-60.
7. Koch KM, Reddy NJ, Cohen RB, et al. Effects of food on the relative bioavailability of lapatinib in cancer patients. J Clin Oncol. 2009; 10(27):1191-6.
8. Hutchinson L. Targeted therapies: PARP inhibitor olaparib is safe and effective in patients with BRCA1 and BRCA2 mutations. Nat Rev Clin Oncol. 2010;7(10):549.

13th Annual Symposium of the British Oncology Pharmacy Association

Janis Smy, BSc

Clinical issues and practical guidance on pharmacy-led research were key themes at the 2010 BOPA symposium for UK oncology pharmacists.

Introduction

Manchester, in the north-west of England, was the setting for the last BOPA Annual Symposium held on 15–17 October 2010. For the second year running, the event was run in partnership with the Annual Conference of the UK Oncology Nursing Society; the joint event attracted around 800 delegates, speakers and exhibitors. It was perhaps inevitable, so soon after the UK General Election, that national politics would top the agenda. However, clinical updates on various oncology specialties attracted enthusiastic attendance—with standing room only in several instances. There was also keen interest in topics related to pharmacists' growing involvement in research and development.

It is impossible, in a short report such as this, to do justice to the full 3-day programme, but here are some of the highlights.

Clinical updates

Aspirin and colorectal cancer

Delegates who attended the fascinating presentation by Sir John Burn, Professor of Clinical Genetics at the Institute of Human Genetics, Newcastle University, Newcastle, UK, were given a preview of data from the international CAPP2 (Colorectal Adenoma/carcinoma Prevention Programme) study of hereditary colorectal cancer. The trial, involving more than 1,000 carriers of Lynch syndrome (hereditary nonpolyposis colorectal cancer), has shown that the incidence of colorectal cancer is halved in patients randomised to aspirin (enteric-coated, 600 mg/day) versus placebo (hazard ratio 0.45; $p = 0.03$). A similar trial, using a lower aspirin dose, is planned.

Management of rare cancers

Dr Andrew Brodbelt, Consultant Neurosurgeon, from the Walton Centre for Neurology and Neurosurgery, Liverpool, UK, outlined the challenges of managing glioma, notably the inaccessibility of the tumours for surgery and the limited life expectancy of patients. The future, he said, would be largely dependent on targeted therapies using, for example, nanotechnology, gene therapy and immunisation as well as chemotherapy.

The session on rare cancers included a presentation on cancers of unknown primary (CUP) by Dr Alan Lamont, Consultant Oncologist at Essex County Hospital, Colchester, UK. The outlook for patients with CUP remains poor, with a median survival of less than one year after diagnosis. 'Treatable' CUP syndromes include:

- poorly differentiated midline carcinoma (treat with platinum-based chemotherapy)
- peritoneal carcinoma in women (treat with platinum/taxane chemotherapy)
- axillary adenocarcinoma in women (treat as breast cancer)
- squamous cell cancer neck nodes (treat as head-and-neck cancer).

Rationalisation of chemotherapy

It seems logical to equate chemotherapy dose banding with neat, round numbers, but this assumption was dispelled by Mr Burhan Zavery, Project Lead at the NHS National Advisory Board for NHS Medicines Manufacturing and Preparation. He advised delegates that logarithmic dose banding is safer than the traditional decimal system, even though it creates unexpected dose sequences, e.g. 100 mg, 111.8 mg, 125.0 mg, 139.8 mg. Using a decimal system, e.g. 100 mg, 120 mg, 140 mg, the proportional difference between bands changes as the sequence progresses, which has important implications for the margins of error, particularly at lower doses. Using a logarithmic sequence, the dose band—and hence the margin for error—increases by the same proportion at each step. 'You will be hearing a lot more about logarithmic dose banding over the next few months,' he told the meeting.

Research and development in practice

Following the strong emphasis on pharmacist-led research at BOPA 2009, the 2010 symposium offered several presentations focusing on the practicalities of designing, conducting and reporting trials and audits.

The first of these, by Mr Stuart Spencer, Executive Editor of *The Lancet*, offered useful tips on how to write for submission to a journal. Key features include: a short, precise title; good abstract; good design and methods; clear conclusions; brevity, and adherence to the journal's instructions for manuscript preparation.

Ms Joanne Woolley, Clinical Audit Manager at the Christie NHS Foundation Trust, Manchester, UK, outlined the essential steps—and some of the pitfalls—in clinical audit. One of her key recommendations was to conduct a pilot audit, involving only a few patients, to make sure the right data are being collected, 'otherwise you could get to the end of your audit, and realise that you are missing key details.'

The 14th Annual BOPA Symposium will be held in Glasgow, UK, 14–16 October 2011.

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Fixed-dose versus patient-specific dosing of anticancer agents

It is generally accepted that body surface area (BSA)-based dosing results in significant inter-patient variability. Despite this, BSA-based dosing continues to form the mainstay of dosing strategies for chemotherapeutic agents. This article explores the alternatives available to BSA-based dosing.

Introduction

Dose adjustments for toxicity are often based on population experience, either from a clinical trial setting or clinical experience of the prescriber, but are generally arbitrary. Reductions of 20, 25, or 30% are used in the face of unacceptable toxicity yet, in the absence of toxicity, doses are rarely, if ever, increased. When this is coupled with widespread *ad hoc* alterations such as dose capping, based on body surface area (BSA) or body mass index, and arbitrary dose adjustments for elderly, less fit patients, the concern is that many patients are under or overdosed. A recent abstract [1] from the 2010 ASCO meeting highlighted the extent of the problem by evaluating a number of drugs: oxaliplatin, cisplatin, doxorubicin, irinotecan, paclitaxel, and 5FU. Fifty per cent of patients did not achieve the target plasma concentration and an equal number were over and under target.

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The evidence for such dose adjustments is scant and in a number of cases have been shown to be erroneous and negatively impacted on patients [2, 3]. The question must therefore be: can we continue to dose chemotherapy according to BSA? And, if we cannot, what alternatives exist?

Individualised dosing

In an ideal world we could use therapeutic drug monitoring (TDM) to adjust doses, maximising efficacy whilst minimising toxicity; unfortunately, this is not an ideal world. Our understanding of the complexities of chemotherapy agent pharmacokinetics (PK) and pharmacodynamics (PD) in clinical practice is minimal. With one or two exceptions we are still 'in the starting blocks' with TDM. Indeed, controversy remains over the use of TDM for imatinib in clinical practice [4]. Other problems exist:

- technology available is limited
- agreement on what should be measured
- need for simple, accurate and timely measurements
- cost
- complexity of combination therapy and scheduling.

It is important that these limitations do not restrict our investigations of TDM. It may mean that only a limited number of drugs can be monitored, or alternatively that we restrict TDM to specific populations:

- adjuvant therapy
- treatment with curative intent
- patients with a phenotype or genotype which is known to alter drug PK or PD.

Such a strategy could focus our research on those likely to gain the greatest benefit initially, whilst generally increasing our understanding of TDM in general for the wider patient population. We have to accept that advances in TDM, for anticancer agents, have been and are likely to continue to be, slow.

Population-based PK modelling, i.e. utilising data from large numbers of patients can be used to determine dosing levels and schedules better. Not only that, it can also elucidate those factors likely to have greatest impact on variability and, once again, target those individuals for whom individualised dosing is likely to have a greater benefit.

TDM in clinical practice is primarily for the antimetabolites [5], population PK modelling has been applied to carboplatin and cladribine [6]. If TDM does not currently provide any additional individualisation of dose, what other strategies can be utilised?

Flat fixed dosing

Giving every patient the same dose, regardless of patient variability, seems attractive, if at first unlikely. The benefits are obvious, including:

- single, or possibly two, ready-to-use doses
- limited pharmacy manipulation
- no dose calculation errors.

It seems unlikely, only because of our experience of interpatient variability with BSA-based dosing. In a comparison of BSA-based and flat dosing of a number of cytotoxic agents there was found to be little difference between the two methods [7]. Historically, flat dosing of some cytotoxic drugs has been accepted, e.g. bleomycin as part of the BEP (bleomycin, etoposide and cisplatin) regimen. Whilst some drugs are debated, the evidence for flat dosing for the monoclonal antibodies is much more convincing [8]; the fact that their PK and PD are less well understood, making TDM almost impossible, and the wide range of dose and schedule in clinical practice for some of them merely add to the support for such a strategy. Indeed, the forthcoming SC rituximab formulation is likely to be licensed as a flat dose, something which is likely to come as a relief to many.

Table 1: Example of number of doses required for two different dose band limits

Drug	Dose/m^2	SA range	Banded dose (+/- 5%)	% of actual dose range	Rounding to +/- 10%		
					SA range	Banded dose	% of actual range
Oxaliplatin	130	1.3	160	94			
		1.31–1.46	180	94–106	1.30–1.53	180	90–107
		1.47–1.61	200	95–105	1.54–1.88	220	90–110
		1.62–1.76	220	96–105	1.89–2.20	270	94–110
		1.77–1.92	240	96–105			
		1.93–2.08	260	96–104			
		2.09–2.20	280	97–103			

For the new targeted agents, flat dosing is becoming the most common strategy, including those in phase I studies. For traditional cytotoxic agents the fact that flat dosing is no better and no worse than BSA-based dosing is unlikely to shift the focus of dosing studies.

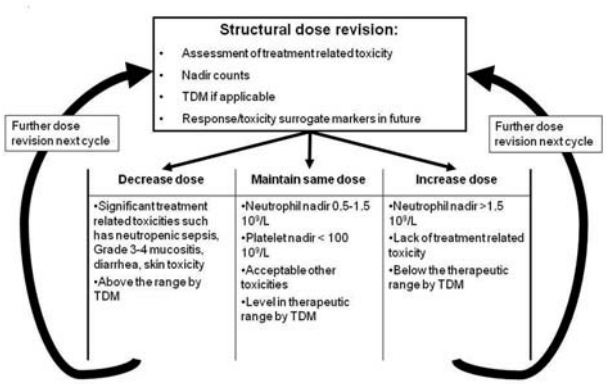
Dose bands/clusters

The limitations of BSA-based dosing and the need to improve the efficiency of cytotoxic preparation led to the development of dose banding [9]. This is where a single dose is applied across a range of BSA, generally with an accepted variance from the calculated dose of ± 5%. This strategy is increasingly accepted in the UK and has been accepted for use within clinical trials. Recently, the use of dose banding in adjuvant breast cancer has shown no impact on toxicity of treatment although the clinical impact of the strategy has still to be determined [10].

Dose banding of many oral chemotherapy agents, e.g. capecitabine and etoposide, requires deviation from calculated doses of more than 5%. If such variations were acceptable for other drugs this would reduce the number of doses required for a wide BSA range to just three, see Table 1. Again, there would be benefits in both preparation of chemotherapy and, ultimately, in treatment capacity.

Similar strategies have seen the use of doses rounded to the nearest vial size, in an attempt to reduce waste [11]. The concern remains that under and overdosing seen with BSA will also apply to flat dosing and banded doses.

Figure 1: Dose adjustment according to response



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This is where the dose cluster strategy comes in. Taking the best of currently achievable, individualised dosing, with the fixed dose and dose band theories it may provide the best solution until TDM becomes more possible.

Gao et al. [12] propose starting with dose clusters, similar to dose bands, with the starting dose determined by patient characteristics—including genotype/phenotype as well as performance status. Where it becomes closer to individualised dosing is the response to first treatment. A range of factors, e.g. neutrophil count, other regimen specific toxicities or clinical responses, are used to determine whether the original dose needs to be increased, decreased or remain the same, see Figure 1. In practice this means the likelihood of over or underdosing is greatly reduced.

The flexibility of this method, which adapts to the knowledge available about PK, PD, toxicity and efficacy, makes it extremely attractive.

What is the role for oncology pharmacists

As oncology pharmacists, it is vitally important that we move chemotherapy dosing forward. We need to push for post-registration studies to better understand how drugs are handled by patients in the clinical setting and, where proven, encourage the use of TDM. For pharmacists involved in clinical trials, the aim should be to encourage novel dosing strategies and approaches to dose adjustment in the absence of TDM. Where arbitrary dose adjustment occurs, we should question the evidence and where such evidence does not exist, encourage research to provide an answer.

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References

1. Rebollo J, Valenzuela B, Duart-Duart M, Escudero-Ortiz V, Gonzalez MS, Brugarolas A. Use of therapeutic drug monitoring of cancer chemotherapy to modify per-protocol doses. J Clin Oncol. 2010;28(15 Suppl e13015).
2. Wright JD, Tian C, Mutch DG, Herzog TJ, Nagao S, Fujiwara K, et al. Carboplatin dosing in obese women with ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol. 2008;109(3): 353-8.
3. Hunter RJ, Navo MA, Thaker PM, Bodurka DC, Wolf JK, Smith JA. Dosing Chemotherapy in obese patients: Actual versus assigned body surface area (BSA). Cancer Treat Rev. 2009;35(1):69-78.
4. Buclin T, Widmer N, Biollaz J, Decosterd LA. Who is in charge of assessing therapeutic drug monitoring? The case of imatinib. Lancet Oncol. 2011;12(1):9-11.
5. Lennard L. Therapeutic drug monitoring of cytotoxic drugs. Br J Clin Pharmacol. 2001;52 Suppl 1:75-87.
6. Lindemalm S, Savic RM, Karlsson MO, Juliusson G, Liliemark J, Albertioni F. Application of popular pharmacokinetics to cladribine. BMC Pharmacology. 2005;5(1):1-8, [doi 10.1186/1471-2210-5-4] .
7. Mathijssen RH, de Jong FA, Loos WJ, van der Bol JM, Verweij J, Sparreboom A. Flat fixed dosing versus body surface area based dosing of anticancer drugs in adults: does it make a difference? Oncologist. 2007;12(8):913-23.
8. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials. J Clin Pharmacol. 2009;49:1012-24.
9. Plumridge RJ, Sewell GJ. Dose-banding of cytotoxic drugs: a new concept in cancer chemotherapy. Am J Health Syst Pharm. 2001; 58(18):1760-4.
10. Jenkins P, Wallis R. Dose-rounding of adjuvant chemotherapy for breast cancer: an audit of toxicity. J Oncol Pharm Prac. 2010;16(4): 251-5.
11. Field K, Zelenko A, Kosmider S, Court K, Ng LL, Hibbert M, et al. Dose rounding of chemotherapy in colorectal cancer: An analysis of clinician attitudes and the potential impact on treatment costs. Asia-Pacific J of Clin Oncol. 2010;6(3):203-9.
12. Gao B, Klumpen HJ, Gurney H. Dose calculation of anticancer drugs. Expert Opin Drug Metab Toxicol. 2008;4(10):1307-19.

Drug interactions in oncology: the impact on cancer care

Suphat Subongkot, PharmD, BCPS, BCOP

Drug interactions are important in the cancer care setting, the majority of drugs being used for palliative care. Failure to recognise these interactions can lead to either overt toxicity or suboptimal treatment.

Introduction

Cancer patients are more vulnerable to drug interactions as they frequently receive multiple medications to alleviate related complications. For drug interactions of all classes, the incidence is estimated to be as low as 3–5% in patients taking small numbers of medications to as high as 20% in hospitalised patients taking 10–20 drugs [1]. Recognising drug interactions as truly related to the suspect drugs, and not to the disease or the environment, is a real challenge.

Table 1: Commonly used drugs in palliative care and potential for interaction

Drug (%)	Frequency of use	Potential for interaction
Anti-emetics:		
Metoclopramide	69	Low
Haloperidol	17	High
Anxiolytics:		
Lorazepam	75	Moderate
CNS stimulants:		
Methylphenidate	80	n/a
Corticosteroids	95	High
Laxatives:		
Senna	41	n/a
Docusate	33	n/a
Lactulose	20	n/a
Opioids:		
Hydromorphone	52	Low
Morphine	30	Low
Methadone	10	Moderate
Miscellaneous:		
Warfarin	7	High
Cotrimoxazole	34	High
Other antibiotics	36	Higher with older agents

n/a: not applicable; CNS: central nervous system

Drug interactions can be categorised in a number of ways. Drug-drug interactions are the most well known and can be pharmacokinetic, pharmacodynamic, or pharmaceutical [2]. Pharmaceutical interactions occur when two or more chemically or physically incompatible drugs are prepared in the same container prior to parenteral administration, resulting in the degradation of one or more drugs. Pharmacokinetic interactions arise when one drug manipulates the absorption, distribution, metabolism, and/or elimination of another drug. Pharmacokinetic interactions via metabolic effects most often occur via drug interactions with cytochrome P450 enzymes. Pharmacodynamic interactions generally result from co-administration of two or more drugs with similar mechanisms of action that result in desirable, undesirable or neutral physiological outcomes.

Although the significance of drug–drug interaction is well addressed, there is less awareness concerning interactions between drugs and nutrients. Pharmacists need to be aware of interactions involving concomitant drugs, newly approved therapeutics and also drug-nutrient interactions. This proactive role will allow pharmacists to prevent all possible interactions of the drug regimens used in practice and hence improve patient care.

Table 2: Some documented cancer-related drug-nutrient interactions

Precipitating factor	Affected object	Finding	Significance/ severity	Recommendation
High-fat meal	Gefitinib	↓ Bioavailability	Unlikely/minor	Take without regard to food
Aprepitant	GI status	Anorexia, constipation,	Unlikely/minor	Monitor GI status
Bortezomib	GI status vomiting, abdominal pain, diarrhoea, constipation	Anorexia, nausea, and monitor/ moderate	Adjust regimen	Monitor GI status
Bortezomib	Volume status	Oedema	Unlikely/minor	Monitor volume status
Bortezomib	Electrolyte status	↓ Serum sodium, potassium, magnesium, calcium	Unlikely/minor	Monitor electrolytes status
Gefitinib	GI status nausea, vomiting, abdominal pain, diarrhoea	Anorexia, stomatitis, severe/moderate	Potentially dosage reduction or loperamide	Monitor, consider
Gefitinib	Hydration status	↓ Hydration	Unlikely/minor	Maintain hydration status
Gefitinib	Electrolyte status	↓ Serum sodium, potassium, ↑ calcium	Unlikely/minor	Monitor electrolytes status
Palanosetron	GI status	Constipation, diarrhoea	Unlikely/minor	Monitor GI status

GI: gastrointestinal

Drug interactions in oncology and palliative care

Typically, most patients diagnosed with cancer are elderly and, in hospitalised cancer patients over 65 years old, each patient was using an average of 5.1 concurrent medications [3]. These conditions grant a situation where drug interactions are more likely to occur. The classes of drugs most frequently used in this setting included anti-emetics, anxiolytics central nervous system stimulants, corticosteroids, laxatives, opioids, anticoagulants, and antibiotics, see Table 1 [4, 5]. Other newer, drugs such as the selective serotonin reuptake inhibitor antidepressants are also increasingly being utilised in this patient population.

Concomitant use of complementary or alternative medicines, sometimes without the clinician's knowledge, can also increase the likelihood of drug interactions.

Drug-nutrient interactions in oncology

A drug-nutrient interaction is described as the consequence of a physical, chemical, physiological, or pathophysiological relationship between a drug and nutrient status, nutrient, multiple nutrients, or food in general [6]. An interaction is deemed significant from a clinical aspect if it modifies the therapeutic effect or compromises nutritional status.

Recently, a few approved cancer-related drugs have been documented for important drug-nutrient interactions and should be monitored closely, see Table 2 [7].

Impact of pharmacists on drug interaction prevention in cancer care

Pharmacists should take steps to protect patients from all types of interaction by positioning awareness and helping educate patients and practitioners. Several measures should be in place at an institutional level including: monitoring therapy and making adjustments once high risk drugs or high risk patients are identified; monitoring the blood level of some interacting drugs with narrow therapeutic index; monitoring some parameters that may help to characterise the early event of interaction or toxicity; and finally increasing documentation of any possibility of interaction encountered via case report or case series for public awareness. These will allow pharmacists to minimise the interaction risk and improve the patient treatment outcome.

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References

1. Nies A, Spielberg SP. Principles of Therapeutics. In: Hardman J, Limbird LE, Molinoff PB, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 9th ed. New York: The McGraw-Hill Companies; 1996. p. 43-52.
2. Beijnen JH, Schellens JH. Drug interactions in oncology. Lancet Oncol. 2004;5(8):489-96.
3. Corcoran ME. Polypharmacy in the Older Patient With Cancer. Cancer Control. 1997;4(5):419-28.
4. Fainsinger R, Bruera E, Watanabe S. Commonly prescribed medications in advanced cancer patients. Presented at the 6th Canadian Palliative Care Conference, Halifax, Nova Scotia, 1995.
5. Bernard SA, Bruera E. Drug Interactions in Palliative Care. J Clin Oncol. 2000;18(8):1780-99.
6. Boullata JI, Barber JR, editors. A perspective on drug-nutrient interactions. In: Boullata JI, Armenti VA, editors. Handbook of drug-nutrient interactions. Totowa, New Jersey: Humana Press; 2004. p. 3-25.
7. Santos CA, Boullata JI. An Approach to Evaluating Drug Interactions. Pharmacotherapy. 2005;25(12):1789-800.

Procedures aid the oncology pharmacy in the preparation and supply of anticancer drugs

Procedures represent a key support for the oncology pharmacy in order to prevent risks and accidents related to handling cytotoxic drugs as well as to provide safe chemotherapy to the patient. This article summarises the key topics that should be addressed when creating/revising these procedures.

Introduction

Handling cytotoxic drugs may represent a risk in the healthcare setting due to exposure to hazardous drugs and may cause severe health problems in all care providers involved in the manipulation of these substances. In 2007, the International Society of Oncology Pharmacy Practitioners (ISOPP) published its 'Standards of Practice' and, in 2008, ESOP released the fourth edition of Quality Standard for the Oncology Pharmacy Service (QuapoS). Both of them collect the requirements for a pharmacy service involved in the preparation of cytotoxic drugs.

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Beginning with these standards of practice, every institution could develop its own policies and procedures regarding cytotoxic handling. Policies are principles, rules, and guidelines adopted to achieve a safe handling of hazardous drugs inside the institution. They have a wide application and are developed in order to avoid or minimise the risk and to produce some benefit. On the other hand, procedures have narrow application, are prone to changes, describe processes and are often stated in detail. Numerous procedures may be developed by the oncology pharmacy in order to describe and control all processes involved in the handling of cytotoxic drugs; the essential topics are discussed in this article.

Cytotoxic drugs handling procedures

Procedures related to hazardous drugs could be divided into several sections, depending on the subject dealing with the manipulation: environment, personnel and patient. Regarding the environment, several issues should be taken into account: facilities, transportation, cleaning, spills, and waste.

Facilities

Manipulation of cytotoxic drugs should be performed in a controlled area and access should be restricted to trained and qualified personnel. Appropriate instructions should be given to the staff in order to avoid inappropriate activities inside the clean room such as introducing food and beverages, eating or chewing, wearing jewellery or cosmetics. It is fundamental to develop a sound monitoring programme to control both biological and chemical contamination of the preparation area. Frequency of monitoring should be scheduled on a regular basis.

Transportation

Delivery of hazardous drugs should be carried out in order to avoid the contamination of personnel and environment; therefore, the oncology pharmacy should set up different procedures regarding external transportation (from the supplier to the pharmacy storage room) and internal transportation (from the pharmacy to the wards). Guidelines should be established for the delivery of compounded admixtures within the hospital.

Cleaning

Several procedures should be developed in order to maintain the cleanliness of the controlled area, particularly for the biological safety cabinet (BSC) or the isolator, the ventilation tool and the disinfection of all materials introduced in the clean room.

Spills

An unpredictable accident may cause contamination of the environment in different settings: during transportation, within the BSC or the isolator, in the clean room or in the store room. A procedure for cleaning and decontamination should be established for each of these situations and a spill kit should also be available. Moreover, a procedure is required to deal with accidental contamination that may involve the patient or personnel.

Waste

The oncology pharmacy should be aware of the risk concerning the contamination of the environment by hazardous drugs. Therefore, it is crucial to develop procedures for collecting the waste after manipulating cytotoxic drugs, along with the material used in the preparation.

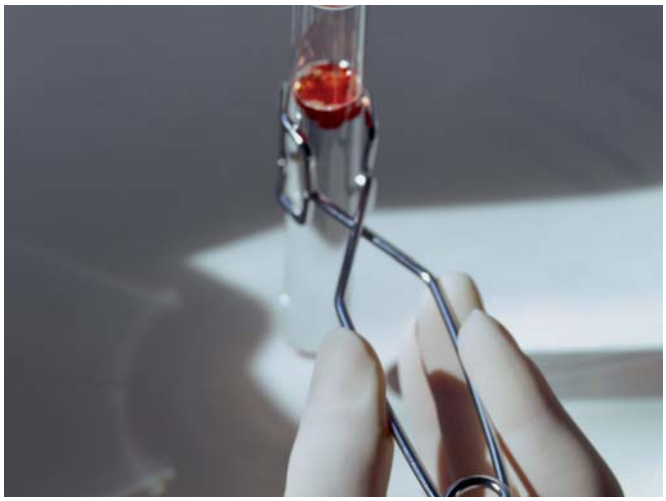
Procedures for personnel should also be developed to assess education, training, clothing, protective measures and equipment.

Education

The staff involved in the preparation of hazardous drugs should be qualified according to local regulations in order to receive proper education concerning risks of exposure to these substances. Educational programmes may be carried out either by internal specialists or by external providers and should be tailored to the skills required for the personnel. Educational courses should be certified as continuing education hours and providers should certify proficiency and attendance for all participants.

Training

Along with education, it is essential that all employees dealing



with hazardous drugs receive appropriate training in the handling of these products at any step of exposure. Personnel should be given all information regarding internal policies and procedures and their regular updates. Validation of training should be performed in order to assess the fulfilment of the required competence.

Clothing and protective measures and equipment
The staff involved in the preparation of cytotoxic drugs should wear suitable clothes and personal protective equipment to ensure the sterility of the product as well as to protect them during any activity dealing with these substances. In the clean room, adequate work breaks should be planned accordingly with the personnel allocation. Scheduled medical examinations and laboratory tests should be offered to all employees who take part in the manipulation of cytotoxic drugs in order to assess exposure to these products.

Regarding the patient, it is mandatory not only to provide a harmless environment in which he/she may receive adequate treatment but also to grant a safe therapy. Consequently, procedures should be focused on the following topics: extravasation, clinical checks and drug preparation.

Extravasation
A multidisciplinary group comprised of oncologists, pharmacists and nurses should develop a policy regarding this subject inside the institution. An extravasation kit containing written instructions, items supplied by the pharmacy and the extravasation documentation sheet should be readily available in the administration area. Pharmacists should prepare and update a list of available vesicants inside the institution.

Clinical checks
Procedures involving clinical checks should be set up in order to reduce medication errors. Ideally, the oncology pharmacist should have complete access to patient's clinical data before reviewing the chemotherapy prescription. For any step of the checking process, signed documentation should be kept for future analysis and monitoring. It is highly recommended that the pharmacist performing clinical checks should not be the same as the person dealing with the preparation of compounded admixtures. Moreover, oral prescriptions should be accurately checked with a similar method used for parenteral chemotherapy.

Drug preparation
Several checks should be completed during the preparation process to assess the volume of cytotoxic drug added to the infusion bag. Independent checks should be carried out by different operators and a pharmacist should validate the final product. Strict procedures should be developed when dealing with drugs that may represent a particular risk, such as to avoid inadvertent intrathecal administration as a consequence of an incorrect preparation and labelling of vincristine.

Documentation related to all procedures should be provided and implemented. Regarding the environment, records should be maintained for chemical and biological monitoring, equipment maintenance, transports, spills, and cleaning. Records concerning the staff should be available for health monitoring, education and training; also, documentation of any extravasation should be kept. Procedures should be updated on a regular basis and reflect any internal or external changes, such as any time a new process is started, when new tools become available or when new risks emerge.

In order to minimise the risk for handling cytotoxics inside the institution, a risk management programme should be developed to establish risk of exposure, exposure control, work organisation and medical surveillance. Once hazardous drugs have been identified, all sources of exposure should be documented and all actions should be established to reduce exposure to these substances. At the same time, work processes should be modified to minimise risks along with the start of medical surveillance.

Conclusion
Procedures are a fundamental tool to implement training of all staff dealing with the manipulation of cytotoxic substances. For oncology pharmacists, they are a unique opportunity to analyse any step in their preparation and to share their expertise with other healthcare providers.

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Sources
ISOPP Standards of Practice: Safe Handling of cytotoxics. J Oncol Pharm Pract. 2007;(13):1-81.
Quality Standard for the Oncology Pharmacy Service with Commentary (QuapoS 4), January 2009.

Chemotherapy dosing in obese patients: the real evidence

Nagwa Ibrahim, PharmD, FAIHQ

Obesity is linked to many disease states including cancer and has been shown to increase mortality. Body surface area is the method used for dosing chemotherapy. This can potentially lead to either increased toxicity or decreased efficacy. Oncologists tend to dose-reduce obese patients despite data suggesting otherwise.

Introduction

The past several decades have been characterised by major changes in life style, leading to a steady increase in average body weight and indices of obesity [1]. Recent research has found that obesity is linked to many diseases, including cancer. They concluded that as the body mass index (BMI) increases by 5 kg/m^2, cancer mortality increases by 10% [2]. Approximately one-third of the world population is considered to be overweight or obese. Overweight is defined as BMI ≥ 25 or < 30 while BMI ≥ 30 is defined as obese [3]. In the US, quality-adjusted life years (QALYs) lost due to obesity increased by 127% from 1993 to 2008, and are now slightly greater than the smoking-related loss in QALYs [4, 5].

The traditional method of individualising cytotoxic drug dose is by using body surface area (BSA) [6], calculated according to the *Du Bois* formula [7]. However, the BSA method of dose calculation was adopted without adequate investigation of the relationship between dose, BSA, and other parameters of body size. In particular, there are no specific dosage recommendations for obese patients undergoing cytotoxic chemotherapy [8].

Unfortunately, drug development and clinical trials in oncology are conducted irrespective of patients' body weight, and obesity is a covariate not usually stratified in data analysis. Therefore, the differing pharmacokinetic parameters of obese patients are frequently overlooked [9]. Obese patients have a greater proportion of fat to total body weight compared to non-obese patients. Theoretically, cancer patients might be overdosed if the chemotherapy dose is based on actual body weight rather than on ideal body weight. Another theoretical reason is the influence of obesity on drug distribution, resulting in prolonged terminal half-lives. However, increased body weight was not associated with increased toxicity in two prospective studies in which obese patients with small cell lung cancer and breast cancer were dosed according to actual body weight [10-12].

Pharmacokinetics in obese patients

Pharmacokinetics (PK) is the study of how the body characteristics such as gender, organ function, or weight affect the time course of drug absorption, distribution, metabolism, and elimination (ADME). Pathophysiological modifications that occur in obese patients may affect parameters such as volume of distribution (Vd) and drug clearance. Therefore, the ADME of a drug is highly unpredictable in obese patients. For instance, increased adipose tissue (body fat) may indirectly alter Vd by impairing regional blood flow to tissue and affecting plasma protein binding. In addition, the more lipophilic an agent, the more likely PK parameters, such as Vd, will be affected. Lastly, the renal function of obese individuals is often altered resulting in decreased drug clearance [9-13].

The PK of some agents has been studied. Rodvold et al. studied the effect of obesity on doxorubicin clearance in 21 adult cancer patients. Patients were divided into three groups: normal (% ideal body weight [IBW] < 115%), overweight (% IBW = 115–130%) and obese (% IBW > 130%). Doxorubicin area under the curve (AUC) was significantly greater in obese patients, and no difference in doxorubicin AUC was found [9, 12, 13]. Another study conducted by Lind et al. to study the effect of obesity on the PK of ifosfamide in 16 patients with advanced non-small cell lung cancer. Patients were considered obese if % IBW was ≥ 120%. In the obese patients, a higher median Vd of ifosfamide was observed and resulted in a prolonged terminal elimination half-life. The study data also suggests that ifosfamide distributes into body weight above the ideal body weight implying distribution to adipose tissue [9, 11]. Powis et al. evaluated the effect of body weight on the PK of cyclophosphamide in 16 breast cancer patients. In this study, patients were considered obese if their adjusted body weight (ABW) was > 120% of IBW and < 130% of IBW, or severely obese if their ABW was > 130% of their IBW. Although a significant decrease in the total body clearance of cyclophosphamide was demonstrated to occur with an increase in body weight, there was no change in volume of distribution. Also, an increase in the terminal elimination half-life was observed in this study [9, 10].

The extent to which compounds are affected by obesity depends on the lipophilicity of the drug. In general, more lipophilic compounds are affected to a greater extent by obesity than hydrophilic compounds [14, 15]. The excess of adipose tissue in obese patients has a smaller proportion of water compared to muscle tissue.

Carboplatin is a platinum compound mainly eliminated by the kidneys. Carboplatin clearance appears to be directly related to the glomerular filtration rate (GFR) and several dosing formulae have been suggested to calculate carboplatin dose. The Calvert formula [dose = target AUC x (GFR + 25)] is the most widely used formula. The GFR is often substituted by the calculated creatinine clearance (CLcr). CLcr = 1.23 x (140-age) x weight x 0.85 (if female)/serum creatinine.

Carboplatin is hydrophilic in nature and would, therefore, not distribute well through adipose tissue. Thus, carboplatin would

not be expected to be influenced by obesity to a great extent [14, 15]. Corine et al. conducted a study to determine the potential utility of alternative weight descriptors in the Cockcroft-Gault equation to predict carboplatin clearance more accurately in overweight and obese patients. They concluded that the use of adjusted ideal body weight (IBW + 0.4 x [ABW-IBW]) in the Cockcroft-Gault equation results in the best prediction in overweight and obese patients [15].

Conclusion

Based on the published, peer-reviewed clinical trials, the data to date have suggested that ABW for dosing chemotherapy is safe and associated with improved outcomes. Confirmatory studies are warranted to successfully implement this change into current oncology clinical practice. In addition, there is very limited data to support the perception that capping the doses of obese patients is beneficial and it is more likely that this practice has negative implications on survival outcomes.

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References

1. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol. 2002;3(9):565-74.
2. Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and guidance. Curr Oncol Rep. 2011;13(1):71-6.
3. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008; 32(9):1431-7.
4. Jia H, Lubetkin EI. Obesity related quality-adjusted life years lost in U.S. from 1993 to 2008. Am J Prev Med. 2010;39(3):220-7.
5. Danaei G, Vander S, Lopez AD, Murray CJ, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366(9499):1784-93.
6. Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. J Clin Oncol. 1996;14(9):2590-611.
7. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Nutrition. 1989;5(5):303-11.
8. Abdah-Bortnyak R, Tsalic M, Haim N. Actual body weight for determining doses of chemotherapy in obese cancer patients: evaluation of treatment tolerability. Med Oncol. 2003;20(4):363-8.
9. Hunter RJ, Navo MA, Thaker PH, Bodurka DC, Wolf JK, Smith A. Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). Cancer Treat Rev. 2009;35(1):69-78.
10. Powis G, Reece P, Ahmann DL, Ingle JN. Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. Cancer Chemother Pharmacol. 1987;20(3):219-22.
11. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson PM. Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution. Cancer Chemother Pharmacol. 1989; 25(2):139-42.
12. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. J Clin Oncol. 1988;6(8):1321-7.
13. Cheymol G. Effects of obesity on pharmacokinetics: implications for drug therapy. Clin Pharmacokinet. 2000;39(3):215-31.
14. Blouin RA, Warren GW. Pharmacokinetic considerations in obesity. J Pharm Sci. 1999;88(1):1-7.
15. Ekhart C, Rodenhuis S, Schellens JH, Beijnen JH, Huitema AD. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol. 2009;64(1):115-22.

Establishing cost-effectiveness of genetic targeting of cancer therapies

The clinical benefit of a new genomic instrument, the 70-gene signature for breast cancer patients, is being evaluated in a randomised clinical trial. The early, controlled implementation process is supported by a Constructive Technology Assessment to help decision-making in an uncertain time of development.

Treatment for patients with cancer has shifted from administering broadly toxic drugs towards fine-tuning of therapies that are targeted to the personal characteristics of specific tumours. An example of this development is the possibility to base the decision of adjuvant systemic therapy for breast cancer on the results of a genomic prognostic profile. The majority of early stage breast cancer patients, particularly with lymph node-negative disease (60–70%), have a fairly good 10-year overall survival with loco-regional treatment alone, with only 30–40% developing distant metastasis [1]. Nevertheless, according to current guidelines, most lymph node-negative breast cancer patients are offered chemotherapy, causing an important percentage of overtreatment [2]. Overtreatment is associated with adverse effects and high costs, however, is understandable with the lack of a fully accurate method to select high risk patients needing chemotherapy. In 2002, researchers at The Netherlands Cancer Institute (NKI, Amsterdam, The Netherlands) identified a 70-gene prognosis signature (MammaPrintTM), using microarray analysis for lymph node-negative breast cancer patients [3]. Using the 70-gene signature, the selection of patients that will benefit most from adjuvant systemic treatment could be more accurate. The signature has been validated in four independent retrospective patient series [4-7]. A prospective feasibility study, the MicroarRAy PrognoSTics in Breast CancER (RASTER)-study was started in 2004 to investigate whether the collection of good quality tumour tissue from community hospitals and the analysis of the 70-gene signature was feasible [8].

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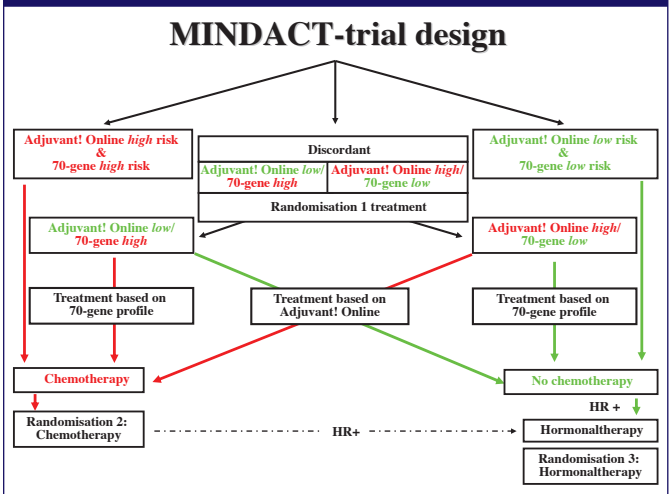
Genomic knowledge leads to the introduction of new and increasingly personalised diagnostics and treatments, which lead to even more complex evaluation designs when following common and accepted assessment practices. Thus, it would take at least 8–10 years to bring the 70-gene signature into clinical practice, via the usual path of prospective trials. For these reasons, we chose to carry out a controlled introduction of the 70-gene signature, supporting the RASTER-study with a comprehensive technology assessment, which takes technology dynamics into account, and decided to perform a Constructive Technology Assessment (CTA). CTA is based on the idea that during the course of technology development, choices are constantly being made about the form, the function, and the use of that technology [9]. This assessment method is a possible answer to the economic evaluation challenges that new genomic technologies pose.

MINDACT-trial

After the feasibility study the MINDACT-trial (Microarray In Node-negative Disease may Avoid ChemoTherapy) was designed. The MINDACT-trial will evaluate whether use of the 70-gene signature is associated with clinical benefit. It will provide findings on the exact prognostic and predictive value of the 70-gene signature. The randomised controlled design allows a defined group of patients (age 18–70, node-negative, operable breast cancer) to have their treatment determined on the basis of either the 70-gene signature or standard practice guidelines (see Figure 1). Patients with discordant risk profiles will be randomised to chemotherapy treatment according

Figure 1: MINDACT-trial design



Source: MINDACT-coordinating centre NL

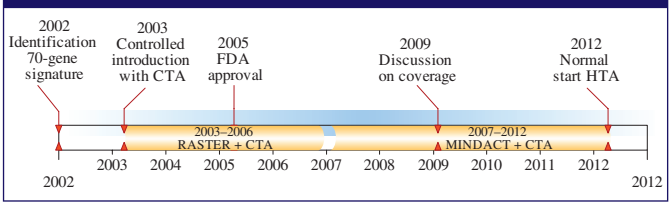
to either the clinicopathological criteria (using the Adjuvant Online software [10]) or according to the 70-gene signature [11]. The trial plans to prospectively recruit 6,000 patients. A follow up of at least ten years will be required before the results are available [12]. The trial started recruiting in 2007 and is expected to finish in 2012. The feasibility of the MINDACT-trial has been proven [13], and the recruitment rate is as planned. The trial is currently ongoing in 10 European countries with 68 participating hospitals.

Constructive Technology Assessment

Coverage decisions regarding new technologies often have to be made at a time when the data on most relevant variables and adequate comparisons are not available yet from high-quality studies. Especially when the promising new technology is in its early development phase and certain stakeholders find reason to speed up implementation in clinical practice, health policy challenges arise. Health Technology Assesment (HTA) is widely adopted to help to manage the introduction and appropriate use of new technologies [14]. However, a HTA generally starts after the technology is stabilised and proved to be valid in clinical trials. During this time many changes in available treatments can occur, which results in a HTA subsequently answering, at least partly, outdated questions [15]. The CTA is related to a HTA, which predominantly implies a cost-effectiveness analysis (CEA) or economic evaluation. CTA also takes technology dynamics into account and has developed from just assessing the impact of a new technology to the analysis of design, development, implementation and interaction of that new technology with its environment. Only a few publications are available describing the application of CTA in health care [15-17]. The aspects studied in this CTA on the 70-gene signature so far were: patient-related aspects (understanding of the 70-gene signature and psychological impact), organisational efficiency (logistics and team functioning) and diffusion scenarios [17]. After the results of the controlled introduction trial were known [8], in The Netherlands a discussion was started as to whether Coverage with Evidence Development (CED) would be appropriate. CED represents a specific approach to coverage for promising technologies for which the evidence is uncertain yet [14], see Figure 2.

For this purpose, first a 'conventional' CEA was conducted. A Markov decision model was used to simulate the 10-year costs and outcomes (survival and quality-adjusted life years (QALYs)) based on a pooled database of three retrospective validation series. When deciding upon the cost-effectiveness of the prognostic tests, the 70-gene signature has a high potential to improve QALY and has the highest probability of being cost-effective.

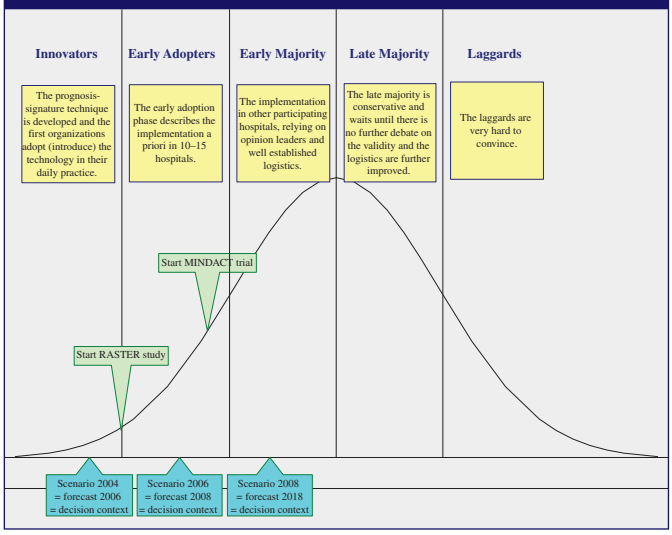
Figure 2: Timeline implementation 70-gene signature



Scenarios

Scenario drafting can be used as a tool in forecasting of new, still dynamic technologies. They are commonly applied in industry to anticipate on future development and diffusion of their products. Scenarios can be used to monitor the implementation process through the various diffusion phases and can support and identify the need for evaluation or even interfere through formal decision-making. In the case of the 70-gene signature, the scenarios were written using the timeline of diffusion phases as described by Rogers' theory, 2003 [18], see Figure 3. These phases reflect the degree of spreading throughout the (medical) society. In the CTA-study, we applied scenario drafting in the case of the 70-gene signature. In the innovation phase, the prognosis signature technique was developed and the first organisations adopted (introduced) the technology in their daily practice. The first scenario was written before the prognosis signature was introduced in The Netherlands (mid-2004). The early adoption phase describes the implementation in 10–15 hospitals. The second, revised scenario was drafted based on the first experiences in the feasibility study (RASTER) in The Netherlands (mid-2006). The early majority phase describes the implementation in a gradually increasing number of hospitals and is ongoing. The 70-gene signature has now been implemented in 25 hospitals in Europe. The third scenario was written at the beginning of the MINDACT trial (mid-2008), in the late early minority/early majority phase. The third draft was written with professional feedback. We designed questionnaires which were sent to 100 European breast cancer experts and organised a consensus workshop in Bordeaux, France. The questionnaires and consensus workshop looked at six patient cases to investigate the compliance with the prognosis profile and

Figure 3: Adoption curve of Rogers' theory, applied to the case of the 70-gene signature



ten different alternatives for the third scenario. The result of the consensus workshop was several probabilities (% of likeliness to happen within the coming 10 years) for the ten different scenarios, see Figure 4.

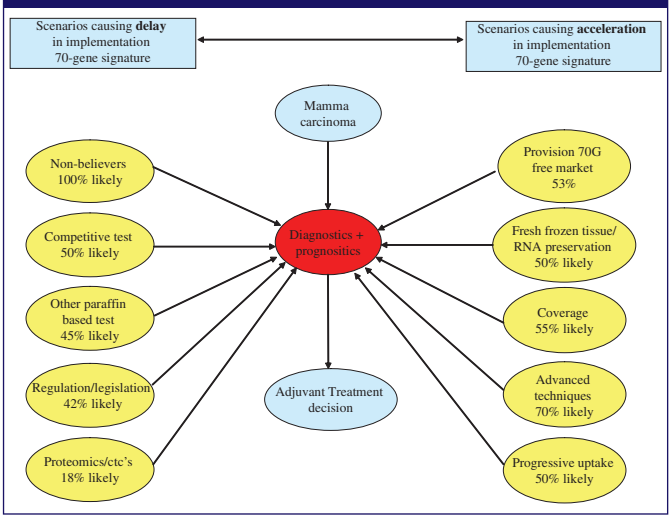
Dynamic economic evaluation

The scenarios drafted on the subsequent phases of diffusion reflect possible 'future worlds' of the use of the 70-gene signature. Probabilistic decision modelling will be used to estimate the cost-effectiveness of the 70-gene signature in these worlds, which may alter as time progresses and more information becomes available. The various alternatives, barriers or facilitators that influence the diffusion of the 70-gene signature will be incorporated into the model as stochastic parameters. Parameters will be updated as soon as new information becomes available. At each moment in time, the decision to adopt or reject the new technology based on existing knowledge, and the decision whether more evidence is required can be informed by the results of the model [19]. Cost-effectiveness Acceptability Curves will reflect the degree of decision uncertainty and value of information (VOI) analyses implies whether additional evidence to further inform the decision is worth gathering, and what kind of information is of the greatest value [20]. VOI is the amount a decision maker would be willing to pay for information prior to making a decision. Finally, the integrated scenarios and VOI analysis reveals factors that warrant intervention in the implementation process in case of the 70-gene signature [21].

Conclusion

Establishing the cost-effectiveness of genetic targeting of cancer therapies is increasingly desirable in an early stage when 'traditional' prospective randomised controlled data are not within reach. In the MINDACT-trial that would take another 8–10 years and future technologies with further personalised differentiation might even lead to conclusions that more qualitative trials will be conducted. However, the challenge is still to inform policy makers about possible advantages or disadvantages and, ultimately, to aid a decision on usage and coverage. A CTA evaluates a new technology in an early and unstable stage of development. Scenarios help to monitor the controlled introduction process and even can assist in anticipating on future developments. Dynamic economic evaluation can support the decision-making, by taking the several scenarios per diffusion phase into account in a decision model. We expect that these methods will prove valuable in combination with more 'traditional' cost-effectiveness analysis approaches.

Figure 4: Result consensus workshop on 10 alternative scenarios



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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687-717.
2. Mook S, Van't Veer LJ, Rutgers EJ, Piccart-Gebhart MJ, Cardoso F. Individualization of therapy using Mammaprint: from development to the MINDACT Trial. Cancer Genomics Proteomics. 2007;4:147-55.
3. Van't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature. 2002;415:530-6.
4. van de Vijver MJ, He YD, Van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Eng J Med. 2002;347:1999-2009.
5. Buyse M,Loi S, Van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst. 2006;98:1183-92.
6. Bueno-de-Mesquita JM, Linn SC, Keijzer R, et al. Validation of 70-gene prognosis signature in node-negative breast cancer. Breast Cancer Res Treat. 2009;117(3):483-95.

7. Mook S, Schmidt MK, Viale G, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. Breast Cancer Res Treat. 2009;116(2):295-302.
8. Bueno-de-Mesquita JM, van Harten W, Retel V, et al. Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER). Lancet Oncol. 2007;8:1079-87.
9. Schot JW. Constructive Technology Assessment and Technology Dynamics: The case of clean technologies. Sci, Technol & Human Values. 1992;17:36-56.
10. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol. 2001;19:980-91.
11. Bogaerts J, Cardoso F, Buyse M, et al. Gene signature evaluation as a prognostic tool: challenges in the design of the MINDACT trial. Nat Clin Pract Oncol. 2006;3(10):540-51.
12. Cardoso F, Van't Veer L, Rutgers E, et al. Clinical application of the 70-gene profile: the MINDACT trial. J Clin Oncol. 2008;26:729-35.
13. Mook S, Bonnefoi H, Pruneri G, et al. Daily clinical practice of fresh tumour tissue freezing and gene expression profiling; logistics pilot study preceding the MINDACT trial. Eur J Cancer. 2009;45:1201-8.
14. Hutton J, Trueman P, Henshall C. Coverage with evidence development: an examination of conceptual and policy issues. Int J Technol Assess Health Care. 2007;23:425-32.
15. Douma KF, Karsenberg K, Hummel MJ, et al. Methodology of constructive technology assessment in health care. Int J Technol Assess Health Care. 2007;23:162-8.
16. Retel VP, Hummel MJ, van Harten WH. Early phase Technology Assessment of nanotechnology in oncology. Tumori. 2008;94:284-90.
17. Retel VP, Bueno-de-Mesquita JM, Hummel MJ, et al. Constructive Technology Assessment (CTA) as a tool in coverage with evidence development: the case of the 70-gene prognosis signature for breast cancer diagnostics. Int J Technol Assess Health Care. 2009;25:73-83.
18. Rogers EM. Diffusion of Innovations. 5th ed. New York: Free Press; 2003.
19. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press; 2006.
20. Claxton K, Cohen JT, Neumann PJ. When is evidence sufficient? Health Aff (Millwood.) 2005;24:93-101.
21. Retel VP, Joore MA, van Harten WH. Conference proceeding. Scenario drafting as a tool to perform early cost-effectiveness analysis: the case of the 70-gene signature in breast cancer. International Health Economic Association, 2009; Beijing, China.

Guideline

Standardised labels for cytotoxics

Shipments of cytotoxic drugs should be labelled for safety. Here we report the results of an ESOP survey about how shipments are labelled in Europe.

Introduction

Highly potent drugs, such as cytotoxics or antivirals, must be handled with caution and their identification during transport is very important to prevent contamination or exposure [1, 2]. For safety reasons, many pharmaceutical companies and wholesalers have started to identify their containers, but drugs are not only conveyed by skilled personnel such as those of these companies, but are also sent by post.

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In 2008, a survey among the ESOP revealed a range of 18 different labels in use, see Figure 1. Different methods of identifying the contents were used and the problem is also compounded when warnings are hidden by postal stickers, see Figure 2. Due to this situation, ESOP suggested using standardised labelling, see Figure 3.

At the January 2008 meeting, ESOP delegates decided to adopt the following: a written warning, 'Highly potent medicine, handle with care'; yellow as a colour code; a unique sign; and a text describing what to do in case of an accident. The yellow hand sign is now also endorsed by the Quality Standard for the Oncology Pharmacy Service with Commentary (QuapoS 4) [3].

Another survey was conducted recently to see how the drugs are shipped and if ESOP recommendations were applied in the different countries.

Method

The second questionnaire, sent in December 2009 to the 29 ESOP delegates, consisted of the six questions below:

Shipment

- Do you receive cytostatic drugs with other medications?

Labelling

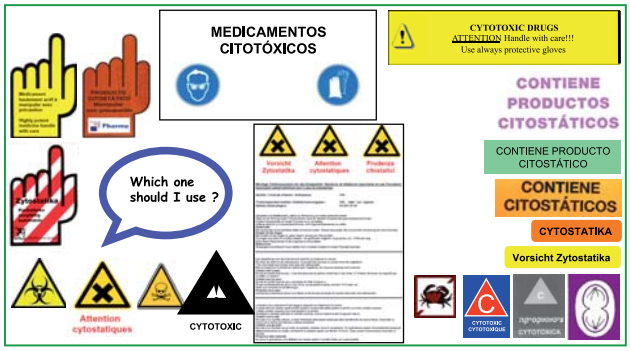
- Are the boxes labelled according to ESOP recommendations?
- If not, is another label used?
- Do you receive unlabelled boxes?

Transport boxes

- Do you receive shipment of cytostatic drugs in leak-proof, sealed cases?
- Do you receive shipment of cytostatic drugs in cardboard boxes?

ESOP delegates had the possibility to answer: always (100%), in most cases (> 50%), in a minority of cases (< 50%) or never (0%).

Figure 1: Labels used for the identification of cytostatic drugs*



*collected by ESOP delegates in 2008

Results

Twenty countries (69%) answered the survey in total. Nine countries always received cytostatic drugs separately, whereas eight mainly received them combined with other medications, see Table 1. Eight always received them labelled, but five received them mostly without and, in one country, cytostatic drug packages were never identified as such. The yellow hand sign was used in ten countries, three of them for all shipments and in seven only by a minority of companies. In four cases, they were always sent in leak-proof boxes.

Figure 3: ESOP proposal: the yellow hand

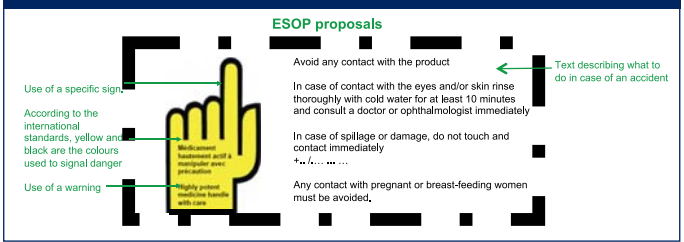


Table 1: Compiled responses to the ESOP December 2009 online survey

Question	Total responses			
	100%	> 50%	< 50%	0%
Do you receive cytostatic drugs with other medications?	2	6	3	9
Are the boxes labelled with the yellow hand?	3	0	7	10
Is another label than the yellow hand used ?	9	2	3	3
Do you receive unlabelled boxes?	1	5	6	8
Do you receive shipment of cytostatic drugs in leak-proof sealed cases?	4	7	5	4
Do you receive shipment of cytostatic drugs in cardboard boxes?	4	5	8	3

The 20 countries that answered the survey were: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Luxembourg, Malta, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, and Turkey.

Figure 2: Warnings hidden by postal stickers

Discussion

These results show that a harmonised identification has not been reached. Only two countries (Austria and Cyprus) always received cytostatic drugs in leak-proof boxes, separated from the other medication and labelled with a warning. The yellow hand sign has been implemented in three countries (Cyprus, Estonia and Finland) and used in a minority of cases in seven other countries. More importantly, many countries make shipments without any specific identification.

The Swiss Society of Public Health Administration and Hospital Pharmacists has written to all pharmaceutical companies and wholesalers suggesting they apply the ESOP recommendations [4], but only one company has implemented use of the yellow hand and one uses it already; the major hurdle being that regulatory and health authorities currently do not recommend the use of a specific identification logo.

Conclusion

Improvement is needed and discussions should be continued to obtain a harmonised European labelling practice.

Acknowledgement

The authors would like to thank all ESOP delegates who answered the questionnaire.

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References

1. Ferguson L, Wright P. Health and safety aspects of cytotoxic services. In: Allwood M, Stanley A, Wright P, eds. The Cytotoxics Handbook, 4th ed. Oxford: Radcliffe Medical Press; 2002. p. 35-61.
2. Jost M, Rüegger M, Liechti B, Gutzwiller A. Sécurité dans l'emploi des cytostatiques. 3rd ed. SUVA, Caisse nationale suisse d'assurance en cas d'accidents; 2004.
3. Quality Standard for the Oncology Pharmacy Service with Commentary (QuapoS 4), January 2009.
4. Letter from the GSASA (Swiss Society of Public Health Administration and Hospital Pharmacists) to the Swiss pharmaceutical firms and wholesalers. January 2010.