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History leads us – the future defines us

Klaus Meier
Editor-in-Chief

EJOP

Nearly 770 years ago the profession of pharmacy was born. The legislation of Emperor Frederick II declared the necessity of the relationship between physicians and pharmacists for better quality in health treatment and economic efficiency.
The purpose even in those times was the best support for patients in all areas of interest.

Today we feel our responsibility grow under this historical commitment to support patients the best. The EU Commissioner for Health and Consumer Policy Mr John Dalli stated in the hearing to the members of the EU parliament "The underlying theme of my work will be Patients First." He said his vision would be that "European Citizens live a longer and healthier life" and that he wanted "well-informed consumers who can take educated decisions on the goods and services they consume".

As his focus is on sustainable health outcomes he will continue to drive action on diseases such as cancer, cardiovascular disease, mental health, age-related diseases and youth health by supporting health empowerment.

Key in Commissioner Dalli's vision is the access of all our European Citizens irrespective of nationality or socioeconomic status to good and timely treatment and to affordable medicines.

He will also be availing himself of the new synergies created by the inclusion of Pharma and Medical Devices in the Health Portfolio. For example, he thinks this can motivate patient-focused research and innovation and can bring new technology to the market at affordable cost to patients and/or health systems across Europe.

Regarding information for patients he believes that patients should have access to information on prescription drugs that are on the market. The inclusion of Pharma in the Health Portfolio gives him the opportunity to reassess the proposal on the table and to inject a stronger patient perspective. He wants to ensure that the single market properly serves the consumer through better access to products and services, both in availability and price. The EU Commissioner will keep a critical eye on how well markets serve consumers and on how the structures may need to change in order to do this better.

Listening to him we understand the importance of the role of pharmacists in the future. As a product- and industry-independent member of the health professionals' team the pharmacist can undertake considerable work not only in the practical part of his work but especially in independent teaching and informing of patients.

In the special field of oncology pharmacy we know that pharmacovigilance makes great demands on the knowledge and ability of pharmacists. The founding declaration of ESOP has only one main aim: to support oncology patients the best.

This new issue of our journal encourages you not only to learn more about new treatment methods but also to recognise our background in the reports of our European activities.

The EU does not have to look far to find people who will take action for their beliefs.

ESOP News

4th Masterclass in oncology pharmacy

Ljubljana, Slovenia, 15–19 November 2010

I am very pleased to announce that this year Slovenia will host the masterclass in oncology pharmacy. The event will be held at the City Hotel in Ljubljana, Slovenia, 15–19 November 2010. The five day course will include quality lectures and workshops, as well as many opportunities for making new contacts, exchanging information and discussing problems encountered at work.

We have put together a programme that will balance the needs of participants for some basic knowledge with some 'hot' topics. So the first part will concentrate on the preparation of antitumour drugs, the requirements of regulatory bodies, the organisation of personnel and facilities and training in aseptic work. We will not miss important issues like stability of drugs, risk assessment, microbiological and technical monitoring. The second part will focus on the work of pharmacists in clinical studies, participation in multidisciplinary teams and giving advice to patients and other healthcare professionals. Among other topics, we will learn about cancer therapy, supportive therapy and updates in oncology and haematology.

Several speakers will contribute from different fields of oncology pharmacy and share their experience with participants. A detailed programme and registration information can be accessed from the ESOP homepage. We are looking forward to hosting you at the oncology pharmacy masterclass in Slovenia!

Andreja Eberl, MPharm – aeberl@onko-i.si

Consolidation radiotherapy in DLBCL after chemotherapy

The current standard treatment for patients with diffuse large B-cell lymphoma (DLBCL) is rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). A retrospective analysis attempted to clarify the role of consolidation radiation therapy (RT) after R-CHOP.

Four hundred and sixty nine patients with histologically confirmed DLBCL were treated between January 2001 and December 2007. The 5-year overall survival (OS) and progression-free survival (PFS) rates for those treated with RT were 91% and 82%, respectively, whereas the OS and PFS for those not treated with RT were 68% ($p < 0.0001$) and 59% ($p < 0.0001$), respectively.

This study therefore showed significant improvements in OS and PFS among patients who received consolidation RT. The researchers suggest that future trials should consider RT again in view of recent advances in delivery techniques, smaller fields of treatment and lower total dose.

JCO Early Release. 2010. Epub ahead of print. doi:10.1200/JCO.2009.27.3441

Efficacy and safety of rasburicase in TLS

According to research in adults with hyperuricaemia or at high risk of tumour lysis syndrome (TLS), rasburicase provides control of plasma uric acid more rapidly than allopurinol.

Rasburicase is effective in controlling plasma uric acid in paediatric patients with haematological malignancies. A study has evaluated the safety and efficacy of rasburicase alone, rasburicase followed by oral allopurinol, and allopurinol alone, in adult patients with haematological malignancies at risk of hyperuricaemia and TLS. The most common serious adverse events were neutropenic infection (4–9%), febrile neutropenia (3–6%), and neutropenic sepsis (1–5%).

The researchers concluded that rasburicase was well tolerated and better than allopurinol in controlling plasma uric acid in terms of rapidity and efficacy. This improvement was observed in patients at high risk of TLS and also in those with hyperuricaemia at baseline.

J Clin Oncol. doi:10.1200/JCO.2009.26.8896

Emerging targets for the modulation of apoptosis resistance in anticancer treatment

Apoptosis resistance is a hallmark of cancer and is linked to treatment failure. Current knowledge of the regulation of apoptosis pathways is reviewed as are biological modulation approaches that may increase the response of cancer cells to therapy.

Introduction

Apoptosis is a cellular death programme that is critical for normal tissue development and the control of tissue homeostasis; it triggers the elimination of unwanted, non-functional, damaged and mutated cells. Defects in apoptosis regulation are linked to a variety of human diseases, including cancer. Apoptosis of mutated cells is an important tumour suppressor mechanism. Tumour cells need to disrupt apoptosis pathways to escape the cytotoxic action of oncogene-mediated and microenvironmental stress during the carcinogenic process [1]. However, the cytotoxic action of classical chemotherapy and radiotherapy includes the induction of apoptosis. Because stress-induced and therapy-induced cell death share similar pathways, the same cellular changes that mediate apoptosis resistance of tumour cells during the carcinogenic process can cause cross-resistance to genotoxic therapies. A detailed understanding of the molecular mechanisms that regulate apoptosis in response to chemotherapy and radiotherapy and of the molecular determinants of apoptosis resistance in tumour cells is a prerequisite for targeting apoptosis resistance of tumour cells in anticancer treatment.

Professor
Verena Jendrossek

The core apoptosis signaling pathways

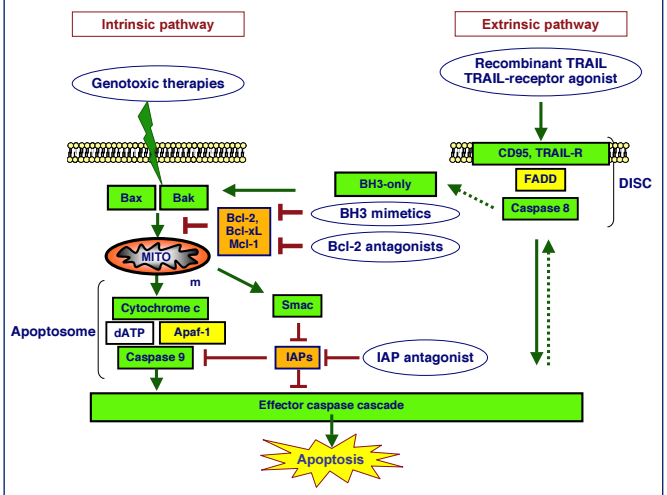
On the cellular level, apoptosis is characterised by the activation of intracellular cysteine proteases, called caspases, which collaborate in proteolytic cascades to kill the cells. Caspases are mainly activated via two distinct but interconnected pathways: the extrinsic, death receptor-dependent apoptosis pathway; and the intrinsic, death receptor-independent apoptosis pathway [2]. The extrinsic pathway is initiated at the cell surface by stimulating death receptors of the tumour necrosis factor (TNF) receptor superfamily, e.g. TNF-related apoptosis-inducing ligand (TRAIL) receptors. Ligand binding triggers rapid receptor multimerization, recruitment of the adapter protein FADD (Fas-associated protein with death domain) and an initiator caspase (mostly procaspase 8) to form the death-inducing signaling complex (DISC) [3]. Proximity of multiple procaspase 8 molecules in the DISC facilitates their autoproteolytic activation. Active caspase 8 subsequently activates downstream effector caspases 3, 6 and/or 7 that cleave a multitude of intracellular substrates thereby provoking apoptosis. If insufficient caspase 3 is activated directly by caspase 8, caspase 8 can co-opt the intrinsic pathway by activating cleavage of the pro-apoptotic Bcl-2 protein family member Bid (see Figure 1).

Chemotherapeutic drugs, ionising radiation or cellular stress mainly trigger the activation of the intrinsic apoptosis pathway. This pathway critically involves mitochondrial changes, e.g. loss of the mitochondrial membrane potential and release of pro-apoptotic factors from the mitochondrial intermembrane space, such as cytochrome c, apoptosis inducing factor (AIF), and Smac/Diablo (second mitochondria-derived activator of caspase/direct inhibitor of apoptosis (IAP) binding protein with low pI). Cytoplasmic cytochrome c triggers the formation of a large cytoplasmic death-inducing complex, the apoptosome, which is composed of cytochrome c, the adapter protein Apaf-1, dATP and procaspase 9. The apoptosome enables the proteolytic activation of caspase 9 that subsequently triggers activation of the effector caspase cascade and finally apoptosis. Caspase 8 or Bid can also be activated downstream of caspases 9 and 3 to amplify the apoptotic signals originating from the intrinsic pathway [4].

Apoptosis is tightly controlled by endogenous proteins. Members of the Bcl-2 protein family function as critical apoptosis regulators at the mitochondrial level [5] (see Figure 1). The Bcl-2 proteins are divided into three classes based on their structure and their pro or anti-apoptotic function. The anti-apoptotic multidomain Bcl-2-like proteins, e.g. Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and A1, share up to four BH domains (BH1-4) and are critical for cell survival. The pro-apoptotic members include the Bax-like multidomain Bcl-2 proteins Bak, Bax, and Bok that share the BH domains 1–3 and constitute the central effectors of mitochondrial permeability transition, whereas the so-called BH3-only proteins (Bid, Bim Bad, Bmf, Bik, Hrk, Noxa) have only one small stretch of amino acids in common and communicate pro-death signals under conditions of cellular stress.

Pro- and anti-apoptotic Bcl-2 proteins form homo or heterodimers via BH3 domain-dependent protein-protein interactions to inhibit or activate one other. In the absence of death signals, the Bax-like proteins are kept in check by their Bcl-2-like anti-apoptotic counterparts. Stress conditions lead to transcriptional up-regulation and/or activation of specific BH3-only proteins thereby altering the balance between pro- and anti-apoptotic Bcl-2 proteins by direct or indirect interactions [6-8]. Essentially, all anti-apoptotic Bcl-2 proteins present in a

Figure 1: Apoptosis signaling pathways



Apoptosis signalling involves sequential activation of initiator caspases (caspases 8 and 9) and effector caspases (caspases 3, 6 and 7) by the 'extrinsic pathway' and the 'intrinsic pathway'. The extrinsic, death receptor-dependent pathway is initiated at the cell membrane in the death-inducing signaling complex (DISC) leading to activation of initiator caspase 8. Activation of the intrinsic pathway critically involves Bax/Bak-mediated mitochondrial changes (loss of the mitochondrial membrane potential ($\Delta\psi m$), release of cytochrome c) leading to activation of initiator caspase 9 in a cytoplasmic multiprotein complex called 'apoptosome'. Anti-apoptotic members of the Bcl-2 protein family suppress the activation of Bax and Bak, whereas the pro-apoptotic BH3-only proteins promote apoptosis either by a direct interaction with Bax or Bak (direct activation model), or by binding to their anti-apoptotic counterparts thereby releasing Bax-like effector proteins (indirect activation model). In contrast, anti-apoptotic proteins of the inhibitor of apoptosis proteins (IAP) family impair the activity of caspase 3 and caspase 9 and thus inhibit apoptosis execution downstream of the mitochondria. Their anti-apoptotic action is suppressed by Smac/Diablo, a protein which is released from the mitochondria when the function of the mitochondria is compromised by the action of Bax and Bak.

Genotoxic therapies induce apoptosis mainly via the Bax/Bak-dependent intrinsic pathway. However their action is inhibited if anti-apoptotic Bcl-2 proteins are overexpressed. Recombinant human TRAIL as well as activating death-receptor antibodies activates the extrinsic pathway and can overcome apoptosis resistance caused by disruption of the intrinsic pathway. BH3 mimetics directly activate Bax or Bak, or neutralise the anti-apoptotic Bcl-2 proteins.

Among these drugs, peptidomimetics of BH3 domains, small molecule BH3 mimetics (bad-like: ABT-737 and ABT-263; pan: Obatoclax), and antisense oligonucleotides that target the mRNA and thus the expression of Bcl-2 (oblimersen sodium) are most advanced in clinical trials. IAP inhibitors can overcome apoptosis resistance caused by IAP-mediated caspase-inhibition.

Green boxes: pro-apoptotic proteins
Yellow boxes: adapter proteins
Orange boxes: anti-apoptotic proteins
Green lines: activation
Red lines: inhibition

given cell have to become neutralised to properly cause activation of Bax or Bak and cell death.

In contrast, the so-called inhibitors of apoptosis proteins (IAPs) such as X-IAP (X-linked inhibitor of apoptosis protein) and survivin, prevent apoptosis execution by inhibiting caspases 9 and 3 downstream of the DISC and the apoptosome [9]. In dying cells, IAPs become inactivated by binding of their endogenous antagonist Smac/Diablo that is released from the mitochondria upon activation of the intrinsic pathway (see Figure 1).

Apoptosis resistance as a target in anticancer treatment

Several mechanisms of apoptosis resistance can be derived from a molecular understanding of apoptosis regulation. On the one hand, cellular changes that affect the expression or function of critical pro-apoptotic proteins such as Apaf-1, Bax/Bak, BH-3 only proteins, or caspases, can prevent the initiation of cell death upon cellular stress. On the other hand, upregulated expression of pro-survival proteins such as Bcl-2, Bcl-xL, Mcl-1, X-IAP or survivin can suppress apoptosis execution [10, 11]. These alterations are frequently found in human cancer and contribute to tumourigenesis, disease progression, therapy resistance, and a poor treatment outcome.

Over the last two decades, much research effort has gone into identifying novel agents that induce cell death in tumour cells that are resistant to chemotherapy and radiotherapy-induced apoptosis or that enhance the efficacy of genotoxic therapies in resistant tumour cells by altering the apoptotic threshold [12, 13]. There is now evidence from numerous preclinical studies that novel agents that target the core apoptotic machinery or endogenous anti-apoptotic factors can reduce tumour growth and increase the efficacy of genotoxic chemotherapy and radiotherapy in vitro and in experimental tumours. Some of these compounds are presently being tested in clinical trials. These include recombinant ligands and activating antibodies of death receptors, e.g. TRAIL-R [3] and Bcl-2 antagonists such as oblimersen, small molecule BH3-mimetics such as ABT-263 and obatoclax [14], and small molecule inhibitors of X-IAP and survivin-like AEG35156 and YM155 [15].

Clinical perspectives

Because apoptosis execution is regulated by a complex network of redundant signaling cascades that display cell type specific expression and activity, a key issue for the rational use of apoptosis targeting drugs as single agents or as sensitising agents in combination with genotoxic chemotherapy and radiotherapy will be the definition of the appropriate patient populations for clinical trials. A precise knowledge of the underlying defects in a given tumour will be critical to avoid the use of apoptosis inducers in cell systems lacking downstream effectors or relevant target proteins. Moreover, any strategy that lowers the apoptotic threshold may increase the

probability of toxic side effects in normal tissues, in particular if specific anti-apoptotic proteins are required for the survival of these cells. Therefore, there is an urgent need to define biomarkers for patient selection that predict target deregulation and the ability of a given tumour to respond to target inhibition by cell death execution. Moreover, selecting apoptosis-targeting agents that predominately induce cell death in tumour cells while being less toxic to normal tissue cells seems mandatory. Finally, it will be necessary to develop strategies to monitor the therapy response and to carefully dissect putative differences in the sensitivity of cancer cells and normal tissue cells to these apoptosis modulators to avoid unwanted adverse side effects.

Although the use of apoptosis-targeting agents is not likely to be a universal approach for all cancers it will certainly guide innovative strategies in anticancer treatment and hopefully increase patient survival in the future.

Visit www.copewithcytokines.de for further information on apoptosis.

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Drug treatment of epilepsy in people with brain tumours

Seizures are a distressing result of many brain tumours, but treatment is not easy, with drug interactions and side effects occurring commonly. A recent trend is to use non-enzyme-inducing anti-epileptic drugs but their place in treatment has not yet been established.

Introduction

Seizures are a common symptom of brain tumours. Between 30–50% of people with high grade gliomas or metastases and 60–90% of people with low grade gliomas will experience seizures during the course of their illness [1]. In theory, the management of epilepsy caused by an underlying brain tumour should not differ from the management of epilepsy due to any other cause. However, it is becoming increasingly apparent that additional thought may need to be given to the choice of anti-epileptic drug (AED) prescribed to people with brain tumours. One of the main reasons for this is the potential for interactions between AEDs and other concurrently prescribed drugs including chemotherapeutic drugs and glucocorticoids.

Simon Kerrigan
MD

Choice of AED according to seizure type

There is little randomised controlled trial evidence comparing different AEDs from which to choose the AED for an individual patient. The International League Against Epilepsy (ILAE) reviewed the available evidence and issued general guidance about epilepsy of all causes in 2006 [2]. Localisation-related seizures arising from one part of the brain or localisation-related seizures with secondary generalisation are the most common type of seizures experienced by people with brain tumours [3]. The ILAE found evidence to support the use of carbamazepine, phenytoin or sodium valproate as initial therapy for localisation-related seizures but also evidence for gabapentin, lamotrigine, oxcarbazepine or vigabatrin as possible effective monotherapy. The ILAE found less evidence to support the choice of any particular AED for the treatment of generalised seizures, although there was some support for carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate or sodium valproate as possible monotherapy.

Interactions between AED and chemotherapeutic drugs

When faced with the decision of which AED to prescribe for a patient with a brain tumour, thought needs to be given to the other drugs that the patient is or may be receiving and how those drugs might interact. Interactions between AED and chemotherapeutic drugs can result in the delivery of an unreliable dose of either drug. The consequences of this could be inadequate treatment of the underlying neoplasm, poor seizure control or increased toxicity from elevated concentrations of either drug. The mechanisms for these interactions are varied, including effects on protein binding and metabolism of either drug by P450 microsomal enzymes in the liver.

Chemotherapy is generally reserved for the treatment of high grade, more malignant brain tumours (WHO grades III or IV). Based on evidence from an important clinical trial [4], radiotherapy with concurrent and adjuvant temozolomide has become the standard treatment in the treatment of glioblastoma multiforme (the most common type of WHO grade IV tumour). Other chemotherapy drugs used in the treatment of primary intrinsic brain tumours include irinotecan, procarbazine, CCNU and vincristine.

Some chemotherapy drugs are processed by P450 microsomal enzymes and induction of these enzymes by an enzyme-inducing anti-epileptic drug (EIAED) such as phenytoin could theoretically lead to a reduction in the effective dose of the chemotherapeutic drug. Many of the newer AEDs are thought not to induce the P450 microsomal enzymes [non-enzyme inducing anti-epileptic drugs (NEIAEDs)] (see Table 1). There is evidence that EIAEDs do decrease levels of a number of chemotherapeutic drugs used in the treatment of CNS neoplasms including nitrosureas, CCNU and irinotecan [5, 6]. There is, as yet, no firm evidence that temozolomide is metabolised by P450 microsomal enzymes and the potential for interaction between temozolomide and EIAEDs appears limited. Sodium valproate is a very commonly prescribed NEIAED but it inhibits hepatic enzymes. So it could potentially increase levels of chemotherapeutic drugs metabolised by hepatic enzymes. Concurrent prescription of sodium valproate has been shown to increase the toxicity of various chemotherapeutic drugs including nitrosureas [7].

Table 1: Enzyme-inducing and non-enzyme inducing AEDs

EIAED	NEIAED
Carbamazepine	Gabapentin
Phenytoin	Levetiracetam
Phenobarbital	Lamotrigine
Topiramate (weak inducer)	Vigabatrin

Effect of drug interactions on survival

If EIAEDs can reduce the effective dose of chemotherapy

drugs, does this translate into an effect on survival? A retrospective review of patients receiving adjuvant chemotherapy for brain tumours (mostly lomustine) revealed a significant decrease in survival with concurrent use of EIAEDs compared to NEIAEDs [8]. On the basis of this evidence, some commentators advocate the use of NEIAEDs as treatment for seizures in people with brain tumours [9]. However, the situation has now been somewhat complicated by the publication of a retrospective review of AEDs use in 620 patients with newly diagnosed glioblastoma multiforme treated as part of clinical trials in the US between 1994 and 2002 [10]. Surprisingly, use of EIAEDs was found to correlate with a better outcome than NEIAEDs. Both overall survival and progression-free survival showed a positive correlation with the use of EIAEDs after adjustment for known prognostic factors of age, performance status, extent of resection, steroid use and baseline neuro-cognitive function. The trials included in the review were carried out before widespread use of NEIAEDs as reflected by the fact that 72% of eligible participants were receiving EIAEDs compared to only 2% receiving NEIAEDs.

Effects of chemotherapeutic drugs on AEDs

In addition to inducing P450 microsomal enzymes, some EIAEDs are themselves partly metabolised by the same enzymes. In turn, some chemotherapy drugs can induce the P450 system resulting in increased metabolism and lower plasma concentrations of AED with potential impact on seizure control. Vincristine, part of the PCV chemotherapy regime (Procarbazine, CCNU and Vincristine) is known to reduce the effectiveness of phenytoin and carbamazepine [11]. Although not commonly used in the treatment of CNS neoplasms, cisplatin and doxorubicin have also been observed to have a similar effect [12].

Interactions between AEDs and glucocorticoids

Many patients with brain tumours receive treatment with glucocorticoids at some point during their illness in an attempt to reduce symptomatic oedema. Dexamethasone is the most commonly prescribed glucocorticoid for patients with primary brain tumours. Phenytoin is known to decrease levels of dexamethasone, possibly through increased metabolism of dexamethasone by induction of P450 microsomal enzymes [13]. Interestingly, concurrent prescription of dexamethasone can lead to either elevated or reduced levels of phenytoin although the exact mechanisms for these unpredictable phenomena are poorly understood. Mean phenytoin levels have been found to be about two times higher in patients not using dexamethasone than in those receiving corticosteroids [14]. This variability supports the monitoring of phenytoin levels in patients who are concurrently receiving dexamethasone.

Side effects of AEDs

Side effects are commonly associated with many AEDs although these can be highly variable and unpredictable. Cognitive deficits are common in people with brain tumours and can be caused by the tumour itself and compounded by the effect of treatments including radiotherapy. Many of the commonly used AEDs are recognised as having potential effects on cognitive function including memory and attention or otherwise causing fatigue and drowsiness (see Table 2). The causes of these symptoms are likely to be multifactorial in people with brain tumours but if particularly troublesome may be an indication to change to a different AED in an attempt to improve quality of life. Other unpredictable side effects include hepatic dysfunction, bone-marrow suppression and skin reactions which can be as extreme as Stevens Johnson Syndrome. Interestingly, skin reactions seem to be more common in people with brain tumours receiving AEDs than people who do not have brain tumours. Other more drug specific side effects have been associated with particular AEDs including visual field defects with use of vigabatrin and speech disturbance with use of topiramate.

Table 2: AEDs potentially causing cognitive impairment, fatigue or drowsiness

Carbamazepine
Gabapentin
Lamotrigine
Oxcarbazepine
Phenobarbital
Phenytoin
Pregabalin
Sodium valproate
Tiagabine
Topiramate
Vigabatrin
Zonisamide

Source: British National Formulary 59

Conclusions

1. Seizures are a common symptom of brain tumours.
2. Anti-epileptic drugs are the main treatment for symptomatic seizures.
3. Interactions can occur between anti-epileptic drugs and other drugs prescribed to people with brain tumours including chemotherapeutic drugs and glucocorticoids.
4. These interactions can result in variable effective doses of drugs being delivered.
5. There has been a recent trend towards the use of non-enzyme-inducing anti-epileptic drugs for people with brain tumours in an attempt to avoid drug interactions, although it is still unclear if potential interactions do translate into a real effect on survival.

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Drug treatment of epilepsy in people with brain tumours

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Association study of rs6983267 at 8q24 with prostate cancer in the Greek population

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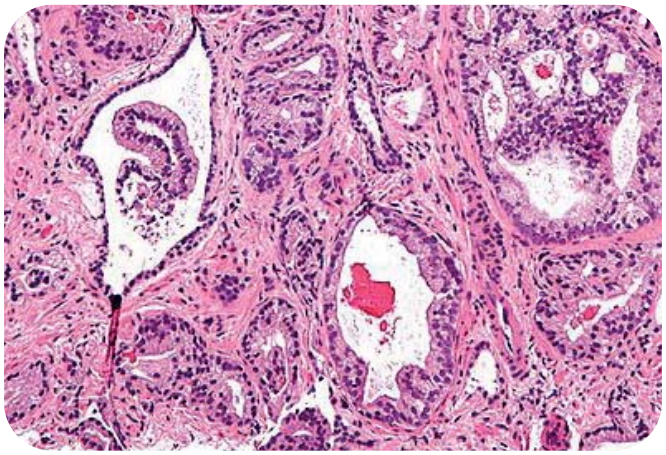
This study aims to determine the frequency of the marker rs6983267 in the Greek population as an independent risk indicator for carriers to develop prostate cancer.

Introduction

Prostate cancer is the most frequently diagnosed cancer in men—the second most common cause of cancer-related male death in the EU [1]. The only firmly established risk factors are age, family history and ethnicity [2]. Men of African descent aged > 65 years, with a first degree relative with the disease are at greater risk than those of European descent with no family history. African Americans are 1.5–2 times more likely to develop prostate cancer, and 2.4–3 times more likely to die from it, than European Americans [3]. Both genetic and environmental factors probably contribute to such differences.



In an attempt to identify genetic variants underlying risk, genome-wide linkage and association studies have been performed and multiple chromosomal regions have been designated to harbour major susceptibility genes for prostate cancer [4]. In men with European ancestry the locus, marked by rs6983267, has shown the highest odds ratio and population attributable risk (PAR) for prostate cancer, compared with other single nucleotide polymorphisms (SNPs) at the same region, with an overall population frequency in northern Europeans of 50% for the at-risk allele [5, 6].

The aim of this study is to determine the frequency of rs6983267 in the Greek population as an independent risk indicator for carriers to develop the disease.

Methods

A total of 208 patients from the same hospital (108 with biopsy-confirmed adenocarcinoma of the prostate and 99 randomly selected controls with no cancer history) participated. Genotyping was performed with melting curve analysis (LightCycler 480) of polymerase chain reaction products from acceptor (5'end-labelled with LCRed 640) and donor probes (3'end-labelled with fluorescein) specific for the polymorphism.

Results

Use of unconditional logistic regression with adjustment for age indicated that the best fitting inheritance model for the rs6983267 is the dominant model. Evaluation of rs6983267 revealed significantly different frequencies in genotypes (OR = 2.83, 95% CI = 1.38–6.00, p = 0.002) and in alleles (OR = 2.06, 95% CI = 1.33–3.02, p = 0.001) between prostate cancer cases and control subjects. Defining exposure as the cases associated with the SNP, PAR % was estimated to be 37.42%, indicating the percentage of disease cases that could have been reduced in the whole population if the exposure was prevented.

In order to combine several risks, e.g. men carrying the rs6983267 with positive family history, we estimated joint PAR % as 43.61%. None of the clinical characteristics in case subjects (aggressiveness of prostate cancer, prostate-specific antigen (PSA) level) were significantly associated with the rs6983267.

Conclusion

Our study confirms the association of rs6983267 at chr8q24 with prostate cancer in the Greek population and indicates the independent risk for carriers to develop the disease. This risk probably has a cumulative effect with positive family history and with other chromosomal regions reported in the literature. For northern Europeans the estimated PAR % of rs6983267 reaches 21%, whereas for the Greek population it is 37%, and has an overall population frequency in northern Europe of 50% for the at-risk G allele, whereas for Greece it is 62%, indicating the greater significance of this SNP to our population [5]. Like that of Zheng et al. [6], our study has not revealed any association of rs6983267 with disease aggressiveness, familial or sporadic forms of prostate cancer or early or late onset. No association between this SNP and serum PSA levels were found, suggesting that rs6983267 is associated with prostate cancer risk directly rather than indirectly, e.g. as a result of increasing the rate of biopsy-driven diagnoses. The use of this marker shows only the risk of developing the disease and has no correlation with clinical characteristics.

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Pharmacometrics in cytotoxic drug dosing – a population-based approach

Dose-finding mathematical models are increasingly being used for cytotoxic drugs with a narrow margin between efficacy and toxicity. Body surface area does not always correlate with dose and studies point to parameters that could usefully be measured in individual patients when deciding the dose.

Population-based pharmacometrics

The dose of a cytotoxic drug is rarely related to the pharmacokinetics or the drug effects. Several mechanisms contribute to the low predictability of a suitable dose but great inter-individual and intra-individual variability play a significant role. Population-based pharmacometrics is a useful way to predict this variability better and to design doses that are tailor-made for the individual patient [1].

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The pharmacometric, or quantitative pharmacology, approach combines pharmacokinetics, pharmacodynamics and statistics in mathematical equations and creates representations, called models, of the links between treatment and observed effect [2]. A population-based study encompasses sources and correlates of variability in, e.g. drug concentrations among individuals who are the target patient population receiving clinically relevant doses of the drug of interest. The population consists preferentially of non-selected individual patients in whom the variation is potentially not only described, but explained [3].

In a population-based study, data from all individuals are modelled simultaneously, and a population model is constructed. The mean values for the pharmacokinetic parameters (or pharmacodynamics) of a drug are harvested from the population model, and the model is able to predict the pharmacokinetic parameters for each individual as the mean population value ± (a subject-specific value + an uncertainty).

The population values are often referred to as the fixed effect and the subject-specific value as the random effect, which contains an uncertainty that is assumed to be normally distributed with zero mean and a variance of ω. Further elaboration on this base model by including covariates can help explain the uncertainty of each individual parameter estimate from the population mean. The covariates can in theory be anything, but should be chosen based on some physiological reasoning or previous knowledge on the pharmacokinetics of the given drug. Most often the chosen covariates include height, weight, sex, age, tumour genetics, other drugs, organ function, etc. The main purpose of including the covariates is to increase the predictive performance of the model by decreasing the uncertainty of the random effects. It may also identify sub-groups of patients and increase mechanistic information about the drug.

The inclusion of covariates in the model requires careful consideration of potential correlation between the covariates. There is, for example, an obvious correlation between the covariates height, weight and body surface area, and very convincing arguments are required to include all three covariates into the final model rather than just one of them, i.e. the most descriptive one, the one that reduces the uncertainty of the parameter estimates most. The down sides to population modelling can be that the modelling procedure is time consuming and complex, and that different researchers working with the same data may end up with different models, e.g. through different interpretations of goodness-of-fit plots, or through different choices of covariates [4]. In this respect, it is understandable that most population pharmacokineticists can quote George Box that "all models are wrong, but some are useful" [5]. This points to the fact that even if different models can be calculated from the same data, there is still scientific justification for performing population-based pharmacometrics, namely that it enables a more accurate explanation of the pharmacokinetics (and/or pharmacodynamics). This in turn may help the clinician in deciding the right dose for each patient.

Pharmacometrics in cytotoxic drug dosing

Population-based methods have preferentially been used to try and predict the best dose for cytotoxic drugs, given pharmacokinetic variability with the requirement for minimum side effects. There are also many other applications where a high variability in response is seen, for instance in the evaluation of pain relief and symptom evaluation in fatigue. Three examples of the applicability of population-based pharmacometrics in oncology and haematology are given.

The first example made a large impact in the field and describes how a consistent model can predict myelosuppression for cytotoxic drugs [6]. In the study, samples were collected for pharmacokinetic analysis after infusions of a range of cytotoxic drugs, and blood counts for leukocytes and neutrophils were performed. A relatively extensive model was

tested including several transition compartments and a feedback mechanism for the effect, i.e. the regeneration of blood cells. A nice correlation was observed for predicted and observed neutrophil and leukocyte counts using the model regardless of the choice of chemotherapeutic agent. The final model may not only help clinicians predict the extent and timing of neutropenia following treatment with these drugs, but also be of great value in predicting myelosuppression in the development of new agents. However, in the study only single drug infusions were tested and the effect in regimens with several drugs was not evaluated. Covariates were not analysed, doing so could potentially increase the predictive performance of the model, and help subgroups of patients to avoid unnecessary high doses that would cause unwanted effects, in this case, myelosuppression.

Another group investigated whether the plasma concentrations of imatinib (Glivec) are correlated with clinical benefit in patients with gastro-intestinal tumours [7]. The pharmacokinetics of imatinib showed a very high inter-patient variability. The authors found that imatinib trough levels at steady state were associated with clinical benefit, and therefore included calculations on both clearance and volume of distribution in the model. By incorporating the effect of two covariates - albumin and white blood cell count, into the final model, they were able to more accurately predict the clearance and volume of distribution despite the high inter-patient variability. The trough concentration at steady state of imatinib could then be calculated for the individual subject.

This clearly shows the advantages of accurately predicted pharmacokinetic parameters. However, before this method can be used in practice, the results need to be validated, and the effective minimum concentration needs to be determined.

In the third case the role of pharmacokinetics in the individual toxicity of BEACOPP was investigated [8]. In the study the pharmacokinetics in a population treated with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone were assayed, where dosing was based on body surface area. Three plasma samples were taken on day one of the three first cycles of therapy. A population-based model was derived in which difference in platelet count was validated with the inclusion of the covariates body surface area, peak etoposide concentration and dechloroethylcyclophosphamide concentration (a metabolite of cyclophosphamide). The chosen model predicted 37% of the variance in toxicity. The conclusions were that phenotyping of the enzyme responsible for cyclophosphamide metabolism (CYP3A4) should be measured in the individual patient, and that the durations of etoposide infusions should be more thoroughly controlled and standardised in order to reduce the variations in peak etoposide concentrations. The authors also noted that even though the dosing was based on body surface area, this covariate was still included in the chosen model and helped reduce overall variance in platelet counts. They argued that this implies that body surface area is not linearly correlated to drug effect. The final model in the investigation may potentially reduce the heterogeneity of haematotoxicity in the BEACOPP regimen and improve the risk/benefit relationship of these drugs.

Conclusion

Population-based pharmacometrics are here to stay. In the years up to 1989 only around 50 articles were published, rising to 240 in 1995–1999; and in the last five years almost 600 articles have been published using population-based pharmacometrics. The important advantage of the method is the possibility of making dose predictions. Predictions can be done from the population characteristics and knowledge of the magnitude of the important co-factors for the dose in an individual patient. The model is also very often used in designing studies in drug development where both dosing strategy and patients can be selected.

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Individualisation of cancer treatment by pharmacogenetics

Pharmacogenetics deals with the factors regulating drug disposition and drug effects due to genetics. In oncology, genetic variations affect response to cytotoxic drugs and may be useful as a guide to treatment.

The concept of pharmacogenetics

The variability of drug effects between individuals, including efficacy, side effects, and toxicity, is a major clinical problem. Apart from environmental factors, inter-individual differences in response to drugs are due to heritable variation in drug disposition and receptor targeting. Pharmacogenetics tries to make associations between heritable sequence variations of DNA (genotype) and outcome of drug therapy (phenotype).

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Pharmacogenetic differences mainly involve genetic polymorphisms of drug-metabolising enzymes or drug targets, such as receptors or intermediate enzymes of specific pathways. Linking gene variations with differences in therapeutic or unwanted effects of a particular drug would enable tailoring of drug and drug dosage based on the genotype of the individual patient. The translation of genotype to phenotype while accounting for environmental factors that influence drug response is a complex task that involves complex statistical analyses and the development of predictive models.

Pharmacogenetic influence on drug metabolism and response

Pharmacogenetics was originally concerned with familial idiosyncratic reactions to the response to drugs, usually regarding toxicity. More recently, different drug metabolising responses related to germ-line polymorphisms have come into focus. One early clinical example was the acetylation of the antituberculosis drug isoniazid, showing a clear bimodal metabolic distribution in the population. Half the number of patients are fast acetylators that have relatively few side effects, whereas the slow acetylators risk suffering from severe side effects such as liver damage, unless the dose is reduced. This capacity for acetylation is an inherited trait. A similar example is the antibacterial sulphonamides, which also are acetylated. In Greenland, the sulphonamides exhibited poor efficacy when introduced due to the fact that most Inuits, the people living in Greenland, were rapid acetylators. The doses given to them were too low to have an adequate effect on their infections.

Several similar examples are known, most of them due to the polymorphism of the genes encoding for the cytochrome P450 isoenzyme. A large majority of drugs, such as antipsychotics, antidepressants, and cardiac drugs, are metabolised by a member of the large cytochrome P450 family. The degradation rate of the anticoagulant warfarin is highly dependent on the *CYP2C9* genotype and its efficacy is also dependent on genetic variations in the gene encoding warfarin's drug target vitamin K epoxide reductase complex subunit 1 *(VKORC1)*. Therefore, important gene-drug interactions of drugs metabolised by these enzymes occur, making genotyping helpful in predicting the elimination of the drug from the body.

Pharmacodynamics is also affected by genetic variability. For example, genetic polymorphisms in the gene for the beta2-adrenoreceptors influence the clinical response to beta2-adrenoreceptor agonists such as salbutamol. Genetic alterations affecting the K^+ channel may increase the incidence of severe cardiac dysrythmias in response to a range of drugs. As mentioned above, warfarin response is determined by genes controlling the blood coagulation process, namely *VKORC1*.

Pharmacogenomics holds promise for assessing drug risks and benefits to prospective patients. Biotechnology companies have developed tests to foresee responses to drugs based on genetic characteristics.

Pharmacogenetics in oncology

The possibilities to treat cancer using different types of cytotoxic drugs have expanded over recent years, yet toxicity concerns and variable efficacy remain shortcomings. One way to overcome these obstacles is to take knowledge of pharmacogenetic variability into account to better predict optimal dosages and tailor drug choice and drug dosages based on germ-line polymorphisms.

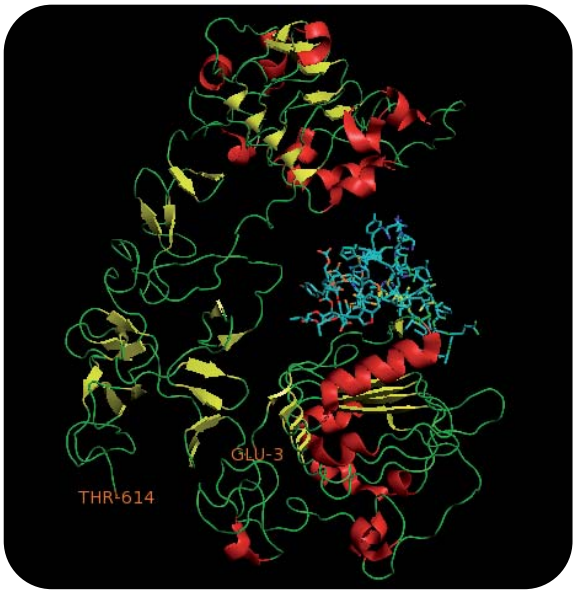
Indeed, in recent years pharmacogenetics in oncology has received intense and increasing interest and some applications coming from the knowledge gained have already reached the clinic. Pharmacogenetics in oncology ideally allows oncologists to individualise therapy on the basis of a genetic test result. Severe toxicity and clinically significant under-dosing may be avoided, whereas predicted non-responders may be offered alternative therapy.

There are several examples of genetic variations influencing the pharmacokinetics and pharmacodynamics of anticancer drugs. These include:

- *thiopurine S-methyltransferase (TPMT)* – enzyme activity to metabolise 6-mercaptopurine in the treatment of acute

lymphoblastic leukaemia (ALL). TPMT is active in several steps in the disposition of 6-mercaptopurine and the enzyme activity is determined by a monogenic trait determined by the *TPMT* genotype. A small fraction of 6-mercaptopurine-treated patients having the v/wt genotype are exposed to severe toxicity, especially leucopenia. The dose in the homozygous-variant patients should be lowered 10–20 fold and in the heterozygous patients having the v/wt genotype the dose should be halved.

- *dihydropyridine dehydrogenase (DPD)* – enzyme activity for 5FU) or capecetabine metabolism. Despite having an allele of < 1% in Caucasians the IVS14 + IG > A variant seems to be one of the key variants resulting in low *DPD* activity and increased incidence of 5FU-related haematologic toxicity.
- *uridine diphosphate glucuronyl transferase (UGT1A1)* – for the glucuronidation of SN38, the active metabolite of irinotecan. A so-called variant 7 tandem TA repeat (instead of 6TA in wild-type patients) in the promoter of the *UGT* gene leads to decreased expression and thus decreased SN38 glucuronidation. The risk odds for neutropenia are increased three to 17 times in a group having the TA7/TA7 genotype as compared to the wild-type patients. However, there are other non-genetic determinants for increased risk for neutropenia/diarrhoea due to irinotecan therapy, such as age > 65 years, co-medication, increased liver transaminases, increased bilirubin, and irinotecan dose schedule apart from the conjugation activity determined by *UGT*.
- *glutathione S-transferase activity (GST)* – for metabolism of platinum-containing drugs or irinotecan.
- *cytochrome P450 2D6 (CYP2D6)* – in the treatment of breast cancer patients with tamoxifen. Tamoxifen forms in two metabolic steps endoxifen, which is 100 to 1,000 times more active than an anti-estrogen as compared to the parent drug tamoxifen. *CYP2D6* plays an important role in this biotransformation. Slow *CYP2D6* metabolisers form less endoxifen which may result in a higher relapse rate and decreased survival in breast cancer patients. The results are still conflicting due to differences in factors such as study design, outcome measures, and classification of genotype.
- *methylenetetrahydrofolate reductase (MTHFR)* and *thymidylate synthase* – in the catabolism of 5FU.



The proof of concept of pharmacogenetics, namely that drug response is a heritable trait, is now generally accepted. However, despite emerging evidence pharmacogenetic testing has not yet found its way into routine patient treatment and care. Replication of earlier findings and validation in prospective trials are required to establish its clinical value and the cost-effectiveness of pharmacogenetic testing. Pharmacogenetic tests and knowledge will likely be in strong demand in the development of new cancer drugs for the future.

The relation of pharmacokinetics-pharmacogenetics to tumour response

The pharmacokinetic-pharmacogenetic influence and importance for drug response is only one side of the coin. At least as large variation is shown by the tumour itself with regard to functioning and genetic make-up. Regarding what can be called tumour kinetics there is a large variation of the tumour microenvironment, perfusion of tissue and tumour, penetration of tumour cells, and influx and efflux transport proteins that determine the access of the drug to the target. Moreover, specific non-heritable, so-called somatic mutations in the tumour are of great importance to drug response. This tumour genetic knowledge is increasingly used to develop targeted antitumour therapies. Examples of this are: *c-kit* mutations in gastrointestinal cell stromal tumours (imatinib), Philadelphia chromosome-positive CML and ALL (imatinib), *KRAS* mutations in colorectal cancer (cetuximab, panitumumab), and EGFR in non-small cell lung cancer (gefitinib). Genetic knowledge regarding tumours is rapidly increasing and special new anticancer drugs are only given if, based on the patient's genetic make-up, there is a possibility for response. Today, the success of cancer treatment is an interaction of many factors, such as the kinetics and genetics of the drug as well as the kinetics within the tumour along with its genetics. It is possible to estimate the complex interaction using statistical population-based methods, which may suggest a tailored cancer treatment approach in an individual patient.

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The role of the oncology pharmacist in the therapeutic decision-making process

Professor Samuel Limat, PharmD, PhD; Virginie Nerich, PharmD

In the increasingly complex field of oncology care, hospital pharmacists should be redefining their role. Their expertise can contribute to decision making in many ways, for example drawing up guidelines, evaluation of daily practices, organisation of care, and the promotion of cost-effective practices.

The systemic treatment of cancer has been evolving constantly for two decades [1]. Many active anticancer agents have become available, covering most clinical situations. With the emergence of targeted therapies and the development of pharmacogenomics, biological and/or cellular parameters are becoming the main factors in therapeutic decision making. Cancer is now considered a chronic disease and many patients can hope for successive lines of active treatment for advanced stages of their disease [2]. So defining the best strategy for each patient is now a complex challenge. In this context, the decision-making process has to be adapted to new parameters and constraints and the role of the oncology pharmacist should be reviewed.

The necessity for, and benefit of, multidisciplinary practice in cancer is accepted. The role of pharmacists in anticancer drug compounding is undisputed. Their place in drug monitoring and prevention of medication errors is also accepted [3]. On the other hand, looking at the literature, the involvement of pharmaceutical expertise in therapeutic choices is scarcely considered, with the exception of pilot studies in supportive care [4, 5]. Considering the complexity of appropriate use of drugs in cancer, the position of oncology pharmacists in decision making should be complementary and useful to oncology practice. Their expertise can be developed in many directions contributing to decision making: drawing up guidelines, evaluation of daily practices, organisation of care, and promotion of cost-effective practices [6].

The definition of appropriate use of drugs is a major challenge in cancer. With intensive clinical research in the area, available data have dramatically increased. Daily practice has to be related to evidence-based medicine [7]. Although several therapeutic options are frequently open to the clinician, randomised clinical trials are not always accessible. A recent review showed that the pertinent information about efficacy was reported in less than half of publications on the most common tumours such as lung, breast, colorectal and ovarian cancer [2]. Although strategy trials, including successive treatments, are now mandatory in metastatic situations, a large body of published data remains related to drug trials. Finally, as off-label use of drugs appears to be inevitable in cancer, it should be controlled and justified [8].

In France, several cooperative, multidisciplinary studies have compared daily practice to published data in solid tumours. Recently, we conducted a retrospective study in two specialised centres, including 1,561 consecutive adult patients with solid tumours [9]. Although off-label use amounted to 33% of cases, 78% of observed treatments were supported by results of phase II (4%) or phase III (74%) randomised trials at the time of use. Furthermore, 20% of additional use was supported by one (4%) or several (16%) positive phase II trials. Finally, the level of questionable use was limited to 2% of cases in this study. The multivariate analysis showed that level of evidence of individual choices was significantly dependent on type of tumour ($p < 10^{-3}$) and stage of disease ($p < 10^{-3}$). In another study, Debrix et al. likewise estimated the level of questionable use at 2%, based on the opinion of an independent expert committee [10]. These multidisciplinary studies, conducted by pharmaceutical teams, confirmed the limits of official labelling of drugs and the necessity for professional guidelines. Recently, a medical and pharmaceutical committee has been set up by the French National Cancer Institute [11]. Its objective is to define guidelines for appropriate use of anticancer therapies. This is a particular challenge for advanced stages and uncommon cancers. Interestingly, these guidelines include off-label use supported by a sufficient level of evidence.

The difficulty of applying published guidelines in daily practice is widely demonstrated in health care. In France, payments for expensive hospital therapies, such as anticancer drugs, are now conditioned by national guidelines. The oncology pharmacist may have a considerable role, especially in organising care. In local settings, a register of valid chemotherapy schedules is mandatory for each tumour, linked to electronic prescribing [5]. The same objective of standardised practice is now being set within regional oncology networks [12]. Oncology pharmacists are allowed to take part, indeed they are invited to coordinate these actions, which contribute to promoting standard guidelines in daily practice. For instance, in the Franche-Comté area (1.2 million inhabitants), our pharmaceutical team is mandated by the regional oncology network to coordinate the regional guidelines committee, as well as to evaluate the conformity of daily practice to several guidelines. Additionally, as use of outside guidelines appears to be inevitable in oncology, these situations have to be assessed and benchmarked by multidisciplinary teams, including oncology pharmacists.

The last area favourable to develop pharmaceutical expertise in decision making is pharmacoeconomics. If new therapeutic

options significantly improve the prognosis for diseases, the costs of treatment are dramatically enhanced. Economic benefit/cost studies are required to optimise the consumption of healthcare resources. Cost-effectiveness data should be integrated into the decision-making process [2]. While the number of published studies has increased in cancer treatment, the number of pharmacoeconomics studies remains low [13]. The use of economic evidence in decision making appears to be uncommon [14]. It seems that these studies are still considered a brake to medical progress. Additionally, their results often fail to represent daily practice [2]. The oncology pharmacist has to develop more pragmatic and comprehensive economic studies, if we are to influence decision making. For instance, areas ripe for investigation include the economic impact of overall treatment strategies, alternative schedules or the advantages of ambulatory chemotherapy [15].

In conclusion, the appropriate use of anticancer treatments is a common objective, from both the patient and the health authorities' point of view. Oncology pharmacists can play a decisive role, from drawing up guidelines to evaluating daily practice. Our challenge is to legitimise pharmaceutical expertise within multidisciplinary care.

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Difficult decisions in the cost-effectiveness analysis of new cancer treatments

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The value of cancer treatment varies. In The Netherlands ENDO was formed to reach consensus on the value of treatment with a newly developed tool. Professors Willemse and Tjan-Heijnen, former chairs of this committee, together look at the intrinsic difficulties of valuing new cancer treatments.

Over the last decades numerous new antitumour drugs have been introduced into routine clinical practice, and more have yet to come. Without exception drugs approved by EMA have also been approved in The Netherlands. In the view of some Dutch critics, new drugs are approved too soon, while over the past years softer, surrogate endpoints such as progression-free survival (PFS) have been replacing hard endpoints, for instance, overall survival (OS). Moreover, cancer centres have become troubled by the high cost of new treatment options for terminal cancer patients as drugs often prove too expensive, since no price-limits have been set. Some centres have even decided to abstain from certain indications, e.g. bevazicumab in colorectal or breast cancer, as increases in PFS have thus far been reported without substantial survival gains.

What is PASQUIL?

In 1998 the Dutch Association for Medical Oncology, NVMO, was founded and in 1999 a committee for the evaluation of new drugs in oncology (ENDO) was established. The assessment of eligibility of new treatments, gauged by budgetary constraints, led to important differences in patient access (postcode medicine). It was, therefore, the intention that a strong and united voice of medical professionals with patient care responsibility would make recommendations to those involved in reimbursement decisions, e.g. the Ministry of Health or the National Health Insurance Board.

For the evaluation of new drugs, rules were developed based only on comparative phase III studies. The subsequent algorithm, called PASQUIL, was accepted by the members of NVMO and comprises specific criteria for **P**alliative treatment, **A**djuvant therapy, **S**ide effects, **QU**ality of life, Impact of treatment and **L**evel of evidence and cost. For instance, in the case of palliative treatment, when compared with a placebo-treated or best supportive care control group, a difference of 20% in response was considered sufficient to accept a new drug for routine use in clinical practice. Improvements in PFS, time to treatment failure and OS of ≥ 6 weeks in addition to response rates, are preferable, in increasing order. Treatment duration should not exceed the median number of life years gained (LYG). For adjuvant treatment, at least a 5% difference in five or 10 years OS (depending on tumour type) and/or a Hazard Ratio of < 0.80 compared with control was chosen as the minimal limit of benefit.

As professionals with clinical responsibility it was agreed by ENDO that treatment mortality should not exceed 5%, the incidence of grade 3–4 side effects should remain below 25% and less than 10% should be lasting side effects with an impact on daily living. Furthermore, the quality of life was expressed as a period of stable or improved Karnofsky Performance Status (KPS) of a minimum of six weeks. The impact of treatment was considered as the number of admission days or outpatient treatment cycles necessary for treatment completion (outpatient treatment to be preferred over inpatient treatment). For the minimal level of evidence at least one phase III study was considered sufficient, if published in an authoritative, peer-reviewed journal. When considering the cost of treatment, no specific limits were formulated, and the costs for one month of treatment or for the total (median) duration of treatment in the phase III study are mentioned without commenting on its relative value [1].

PASQUIL in use

Handling the algorithm for the evaluation of new drugs has proven to be awkward in some instances. For example, what to decide if only response data appear to meet the criteria without demonstrated improvements in disease-free survival (DFS) or OS in a tumour so rare and chronic that there will never be a phase III study performed, as for sorafinib in nonmedullary thyroid carcinoma?

Other examples derived from clinical practice include:
The use of bevacizumab in breast cancer was shown to improve DFS up to five months, but OS did not improve significantly, and was even inferior in a group of patients aged over 65. As a result bevacizumab was not approved for reimbursement in Belgium, and only hesitantly in The Netherlands as a first-line treatment in combination with weekly paclitaxel.

The survival data of bevacizumab combined with an irinotecan-comprising schedule in colorectal cancer were impressive in the first study published, and its use was accepted, but when combined with a FOLFOX regimen a survival gain proved non-existent in the successor paper (see also CJ Punt et al., Eur J Hosp Pharm Prac. 2009(15);2:62-5). Discussions are still ongoing as to whether this was as the result of stopping bevacizumab too early, that is, simultaneously with stopping cytostatic treatment and is the subject of an ongoing Dutch phase III study (CAIRO 3).

The tyrosine-kinase inhibitor lapatinib showed an impressive four months increase in DFS in patients with breast cancer in the first analysis, which caused the pivotal study to be put on hold. But this dwindled to less than the minimal six weeks in subsequent analyses, while any eventual differences in survival were obscured by allowing cross-over treatment. For our committee there was still sufficient reason to recommend the drug for routine clinical practice. However, the National Health Insurance Board, advised by its technical committee CFH (Committee Pharmaceutical Help) decided negatively on its reimbursement [2].

The efficacy of panitumumab (as well as that of cetuximab) in colorectal cancer was found to be present only in *KRAS* mutation negative patients in a meta-analysis and proved to yield a modest increase in PFS but not OS. We recommended, and the drug was accepted, for routine clinical practice [2], although the gains in PFS were not much longer than the six weeks' minimum. The price claimed for the drug is again prohibitive, but this is also the case for other new drugs which show only modest benefits. Such pricing appears to be set more in accord with the expected average increase in survival they may produce than reflecting the costs of development – a policy which has been called profiteering by some.

Interim analysis, a mixed blessing?

It has become increasingly usual in comparative studies of new cancer drugs to perform an interim analysis after a prespecified number of events and the monitoring committee tend to put a study on hold as soon as a significant difference in surrogate endpoints such as PFS have been found. Subsequently, crossover from control to the treatment arm is often allowed, obscuring an eventual difference in survival.

The use of interim analysis has been praised because in this way treatment results will be available at the earliest moment, allowing all potential patients to derive the benefit of active new drugs for serious conditions as soon as possible, which, of course, is a commendable goal. The producers of these drugs will certainly not object to such a policy, as financial returns will be realised much earlier in this way. But as a result of crossover a relevant difference in survival between the two groups in the study may largely disappear. Similarly, the difference may be obscured by any effective second-line treatment with other drugs. Analysis of study results after censoring of crossed-over patients may introduce a strong bias, because only the less fit patients with a moderate performance status will be analysed. In fact, by preferably including patients who did not reach crossover in the no-treatment arm tends to overvalue the new treatment [3, 4].

Cost-effectiveness analysis

Indeed, if a cost-effectiveness analysis (CEA) is performed in studies such as these, where the survival gains are minimised as result of crossover or other second-line treatments, the calculated costs per quality-adjusted life years (QALYs) can be expected to reach sky-high levels.

It is obvious that the usual methods of calculating a standard CEA will have shortcomings in this setting. Perhaps new rules should be applied if data are less robust and reliable. For example, the calculation of progression-free life years gained or the costs of the total survival period after instituting a specific treatment instead of only survival gains compared with a no-treatment arm, including costs incurred after additional or subsequent illnesses and their treatment.

Another point of concern is the fact that there are no uniform ways to interpret study results and calculate cost-effectiveness. These depend on a great many variables and assumptions made in the analysis of existing data, often so because the time-period over which the data are collected is limited. Extrapolations frequently have to be made in order to derive definite endpoints, such as the OS from data in just over 50% of patients studied over a limited period of time, actually creating a 'black box'. This problem has arisen, for instance, in the CEA performed for NICE in the UK for the evaluation of new drugs in renal cancer. The institute which performed the analysis arrived at an Incremental Cost-Effectiveness Ratio (ICER) of about GBP 100,000 (Euros 117,360). However, when the analysis was repeated by others after an outcry from patient advocacy groups, the final amount proved to be no higher than GBP 50,000 (Euros 58,680), proving acceptable for introduction into the NHS [5].

Quality of life, what should be considered as clinically relevant?

In performing a CEA, it is now usual to express the ICER in terms of LYG, corrected for quality of life (QoL), thereby deriving QALYs. The determination of QoL can be done from an individual or a societal perspective. In the latter case, utilities are chosen as determined by a group of informed lay persons, using standard gamble or 'willingnessto-pay'. In the case of the former methodology, QoL is usually measured by a validated questionnaire, such as the EORTC QLQ-C30.

A major problem with measuring QoL in this way is that, being a subjective measure, it is rather insensitive and slow to change over time, thereby proving unreliable. Changes in QoL have shown 3–6 months lag time compared with more objective measurements such as estimating KPS. Correlation between the self-rated EORTC QLQ scores and KPS scored by investigators usually are not very close [6]. Critics may state that the poor correlation between KPS and self-reported scores may reflect the relatively poor estimation by physicians, but this discrepancy may also be interpreted as over-rating by the patient.

A problem of quite another order is the use of group statistics in patients who are subject to large and diverse changes, some improving but many deteriorating at various rates. We would prefer not to place all these patients together, but to single out those patients with a stable or improving QoL and reflect the time-course of only this group, i.e. the time elapsed

until a certain decline in KPS occurs. Assuming this criterion, a change in KPS to constitute an event, the group with non-deteriorating KPS (time without progression in KPS) can be calculated and shown graphically, mostly demonstrating a close correlation with the PFS curve. This way the change in QoL will mirror the course of disease, make changes in KPS over time clearer and will better reflect the differences between treatments responses in the groups studied.

Another problem is that of missing forms: when patients are deteriorating, the number of questionnaires returned diminishes and several statistical methods have been devised to correct for missing forms. However, in the palliative setting the DFS curve appears to correlate well with the number of questionnaires returned. In our view, measuring QoL in the case of terminally ill patients for the purpose of economic evaluation should be abandoned, as it usually adds little information to the clinical data. Measuring specific domains such as social and emotional functioning will even prove futile when considering changes over time, but maybe will have more meaning when comparing between groups.

New developments in The Netherlands

Since 2006, new, expensive hospital drugs, expected to surpass a limit of Euros 2.5 million drug cost a year, are included in a specific shortlist. These are reimbursed separately to the institution, but only for 80% and if used for the approved/licensed indications. However, the remaining 20% overhead cost may still give substantial financial problems to healthcare institutions and the problem with frequent off-label use in rarer tumours which will never attain a registered indication or their use in second- or third-line therapy, however medically sound it may be, is still not resolved.

Next, for each registered use a CEA of the drug 'in daily clinical practice' is to be performed and data demonstrating the effective use and the cost-effectiveness of the drug should be submitted within three years. This condition, performing CEA after registration, for all drugs on the list, gives rise to several problems, apart from the question of who is going to pay for the research.

First of all, it has been accepted by most researchers in Belgium and The Netherlands that three years for reporting on such an outcome study is too short for many indications. An additional difficulty in the economic evaluation of these expensive drugs is the calculation of cost-effectiveness in a phase IV setting. This is difficult as the incremental benefits are hard to assess in the absence of a no-treatment comparator group. Yet another problem bound to occur is that the indication for any effective drug will be shifting to earlier use, i.e. in less progressive disease, more prone to positive outcome, simultaneously with a shift in the population at hand, usually improving treatment results. Comparison with historical patient groups may introduce bias, as diagnostic methods may improve as well over a 3-year period. This means that the patient characteristics in the start-up period of a new treatment may change significantly. A final caveat could be that effective drugs, such as trastuzumab, are not often used as a single treatment, which will pose the difficult question of deciding which drug within a given combination will carry the most benefit.

Developing and setting limits?

Despite several claims to define thresholds for cost-effectiveness, the Minister of Health in The Netherlands has not stated a financial limit like NICE in the UK. In The Netherlands, the Council for Public Healthcare and Cure has named a limit of Euros 80,000 per QALY as the limit for cost-effectiveness, based on life insurance data and WHO rules indicating a limit of threefold the Gross National Product per capita [7].

When making choices of which drugs to reimburse, it is also difficult to compare endpoints for life-threatening oncologic conditions, e.g. disease progression or survival, with non-fatal events in prevention studies (osteoporosis, non-fatal myocardial infarction, stroke) or in chronic and symptomatic conditions, e.g. rheumatoid arthritis or gastrointestinal diseases, such as colitis or Crohn's disease. Comparing cost-effectiveness for various indications cannot be resolved by considering utilities only, but will also need to consider the urgency or existential threat of progressive and terminal diseases versus other indications. Some have even suggested that in the case of incurable cancers the value of each month should be doubled when calculating CEA, instead of correcting for estimated QoL and utilities [8].

The future

How to reach a sustainable financing of drug costs in an ever increasing price spiral? A new proposal by the Ministry of Health for the years to come is full reimbursement of drug costs for all medicines on the 'expensive drug shortlist', and to allow immediate reimbursement as an 'add-on' for the specific Diagnosis-Treatment Combinations. Drugs will be clustered according to specific indications, and the price of the cheapest drug should then serve as 'leading'. Specific measures should be taken to ensure that hospitals will still strive to provide the most economic alternative. It is hoped that this will help in giving equal quality of care to all patients, and to assure equal access to all who need it.

Conclusion

In The Netherlands access to new and expensive drugs has improved, and to a certain extent some of the financial problems for the care-giving institutions have been resolved. Nonetheless, 20% of drug costs are still not reimbursed and problems with the frequent use of off-label indications have not been addressed properly.

Still, it is difficult to envisage how we can control costs without limiting access to new drugs. Making choices between which drugs and indications to reimburse will in the long run prove to be inevitable. These choices should be made on a

national level, and should incorporate all parties involved, the Ministry of Health, healthcare managers, insurance companies, hospital pharmacists, doctors and patient advocacy groups. Maybe the institution of a specific Committee encompassing all of these groups, as in the UK, will prove to be the most sensible way to handle these issues in a politically most acceptable way for all patients. It will be a difficult task to devise clear rules for this game, so that the 'black box' of basal assumptions in CEA will become transparent and not one of Pandora's making.

The Dutch Association for Medical Oncology has developed rules for drug evaluation, called PASQUIL, to support the selection of new cancer treatments in clinical practice.

In The Netherlands, for drugs on the 'list for 80% reimbursement of expensive medications' a CEA is required after a period of three years. However, a 3-year period may be too short. The rules for performing CEA should be more specific and strict.

As plans are being developed to establish a Dutch equivalent to the UK NICE, comparing cost-effectiveness between drugs can only be decisive if strict rules are followed and politicians are willing to set financial limits.

Measuring quality of life does not add useful value to economic calculations in terminal patients, as it is too insensitive, slow and arbitrary when done from a societal perspective. It may, however, be of value in prevention studies or chronic and symptomatic conditions.

Drug pricing should be controlled better, preferably by a common European institution as an addition or similar to EMA.

The economic evaluation of cancer drugs has received special attention in several oncology journals, which give a good overview of the problems presented here and their socio-economic consequences [9, 10].

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Parenteral nutrition in oncology

Parenteral nutrition has had limited indications in oncology, since most clinical trials have been unable to demonstrate benefits such as improvements in survival rates or quality of life. However, an increased understanding of the pathogenesis of cancer cachexia suggests a new paradigm for its use in cancer patients.

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A progressive deterioration of nutritional status is frequently found in cancer patients [1]. The clinical relevance of malnutrition is underlined by its close association with increased morbidity and mortality. Malnourished cancer patients present with a higher risk of developing severe chemotherapy-associated toxicity, leading to a dose reduction or failure to complete the planned anti-neoplastic therapy [2]. Moreover, malnutrition negatively impacts on the quality of life of cancer patients [3]. It is therefore highly appropriate that prevention and/or treatment of cancer-associated malnutrition is now a clinical priority in oncology.

Pathogenesis of cancer-associated malnutrition: cachexia

The pathogenesis of cancer-associated malnutrition is multifactorial, with evidence indicating that two main catabolic factors are involved; cancer-induced reduction of appetite and energy intake (anorexia), and profound changes in host metabolism [1]. Body weight loss which is induced by caloric restriction activates a number of biochemical pathways protecting body mass by reducing energy expenditure and preserving muscle mass at the expense of fat mass. In contrast, tumour-induced weight loss fails to trigger these protective pathways, and the efficient utilisation of nutrients by host tissues is also compromised. As a consequence, weight loss in cancer patients is unavoidable, occurs rapidly and severely, and although normalisation of food intake by artificial nutrition may improve body weight, it may not restore normal body composition [4]. Indeed, muscle loss remains largely unaffected, and water retention and body fat gain account for the increase of body weight observed during artificial nutrition.

The mechanisms responsible for this are currently being elucidated, but inflammation appears to play a significant role. Cancer cells have the ability to create an inflammatory microenvironment [5]. Inflammation promotes growth, replication and dissemination of cancer cells [5] and may compromise the efficiency of the host defences, facilitating the escape of tumours from immune surveillance [6]. But beyond these effects exerted at the local level, inflammation induces systemic effects as well. As a consequence of the interaction between the tumour and the host, a chronic and low-grade inflammatory response develops [7] which acts to suppress appetite and derange energy metabolism [8], and increase wasting of muscle mass and fat tissue [7]. These molecular and biochemical events translate into the clinical syndrome of cancer cachexia, which should be considered as a specific subset of malnutrition. Indeed, cachexia has been recently defined as 'a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass'[9].

Does it stimulate tumour growth?

Both enteral nutrition (EN) and parenteral nutrition (PN) address only one characterising factor of cachexia, i.e. reduced energy intake, with minimal influence on the tumour-induced metabolic disturbances which reduce the efficient utilisation of substrates. However, an increased understanding of the pathogenesis of cancer-associated cachexia is paving the way for more effective nutritional and metabolic strategies to replenish cancer patients.

The change in eating behaviour of cancer patients is largely due to alterations in brain neurochemistry induced by the growing tumour [8], although the contribution of chemotherapy-induced toxicity on oro-pharingeal mucosa cannot be overlooked in patients with advanced disease. In general, the gap between energy requirements and energy intake in cancer patients ranges between 200–400 kcal/day [10]. Consequently, if not corrected, cancer anorexia will progressively contribute to the onset of malnutrition. To fill the caloric gap, the use of artificial nutrition is an intuitive solution. In particular, the use of PN appears best suited to overcome the reluctance of cancer patients to eat and to by-pass the psychological distress related to the insertion of the feeding tube. On the other hand, the concern of the possible stimulation of tumour growth remains unresolved and limited evidence exists showing any benefit for PN in cancer patients. However, recent data may help to dissipate these uncertainties.

A direct effect of PN on tumour cells' replication rate has not been consistently demonstrated in clinical trials. In a recent review, 12 studies evaluating tumour growth in patients receiving nutritional support were examined [11] with tumour growth reported to increase following artificial nutrition in seven of the studies [11]. The lack of consistency in the literature could be explained by the different nutritional regimens and by the heterogeneity of the cancer patients enrolled in these studies. Indeed, recent data demonstrate the importance of the genetic profiles of human cancers not only when explaining their susceptibility to

chemotherapy, but also when trying to give general recommendations regarding nutritional support during tumour growth. The metabolism of cancer cells is mainly based on aerobic glycolysis, since they frequently lack key enzymes for fat oxidation [12]. Consequently, the infusion of glucose by PN may well stimulate tumour replication. However, the susceptibility of cancer cells to the negative effects of dietary, and particularly glucose restriction is not ubiquitous, but linked to specific mutations within the glucose metabolism pathways. Cancer cells forming dietary-restriction-resistant tumours carry mutations causing constitutive activation of the phosphatidylinositol-3-kinase pathway [13]. Therefore, a general recommendation suggesting the avoidance of PN in cancer patients would benefit only those patients whose tumours have those specific mutations. To overcome this uncertainty, the infusion of a lipid-based PN (70–100% of calories provided as lipids) or the prescription of a ketogenic diet with minimal content of carbohydrates have been proposed [14]. Whether a lipid-based PN should represent the standard approach remains unanswered. Moreover, recent experimental evidence demonstrates that glucose deprivation contributes to the development of mutations in cancer cells which favour their survival in hypoglycaemic environments [15]. Therefore, withholding of PN in cancer patients should not be based on the fear of stimulating tumour replication rate, since cancer cells may be genetically equipped to escape the negative effects of dietary restriction.

Current standard of practice

As recently reviewed by ESPEN, the European Society for Clinical Nutrition and Metabolism [16], the indications and therapeutic goals of PN in oncological patients are:

- preventing malnutrition/cachexia
- enhancing compliance with antitumour treatments
- controlling some adverse effects of antitumour therapies
- improving quality of life.

However, it must be emphasised that these indications are limited to aphagic cancer patients with gastrointestinal failure. Indeed, there is evidence showing that PN is ineffective and probably harmful in cancer patients in whom oral or enteral feeding is feasible [16]. PN is recommended in patients with severe mucositis or radiation enteritis, and in those patients who cannot meet their energy and protein requirements exclusively via oral diet/enteral feeding [16].

Clinical results support the use of PN in two other clinical settings. Malnourished cancer patients undergoing surgery should receive perioperative PN if enteral nutrition is not feasible [16]. PN is also recommended in cancer patients receiving haematopoietic stem cell transplantation and presenting with severe mucositis, ileus or intractable vomiting [16]. PN should then be withdrawn when patients can tolerate approximately 50% of their requirements enterally [16].

Uncertainties exist regarding the role of long-term PN in cancer patients with intestinal failure, since a number of emotional, philosophical and religious factors may influence the final decision. In general, it is now widely accepted that PN should be offered only if:

- EN is insufficient
- expected survival due to tumour progression is longer than 2–3 months
- it is expected that PN can stabilise or improve performance status and quality of life
- the patient desires this mode of nutritional support.

Nevertheless, the decision is frequently made on a personal basis, thus accounting for the large differences existing across Europe in the number of cancer patients on home PN.

A distinct advantage of PN over EN is its independence from gastrointestinal tolerance, which may limit the digestion and absorption of the enteral formula. Energy requirements of cancer patients vary but 30–35 kcal/kg body weight is generally considered to be sufficient [16]. However, it is important to note that in a few cancer patients not even 35 kcal/kg body weight can maintain body weight [10], thus underlining the need to regularly check patients receiving PN. A few reports suggest that lipid-based PN may confer additional metabolic benefits over conventional glucose-based parenteral mixtures [14], with 60–70% of non-protein calories infused as glucose, the rest being lipids.

A new paradigm

Considering the negative role of tumour-induced inflammation on host metabolism, integration of PN with anti-inflammatory therapy may yield relevant clinical outcomes. Lundholm et al. demonstrated in patients with malignant disease that the combination of nutritional support, including PN, and a cyclo-oxygenase inhibitor resulted in improved energy balance, enhanced maximum exercise capacity and increased survival [17]. This study underlines the relevance of PN in covering nutritional requirements when oral intake and EN are insufficient. Also, it suggests that the integration of standard PN with the infusion of nutrients with specific pharmacological activity including anti-inflammatory properties, i.e. the omega-3 fatty acids, may maintain or restore nutritional status and yield significant clinical results [18]. Other nutrients such as branched-chain amino acids [19], arginine [20], and glutamine [21] could also be of benefit.

Glutamine is the most abundant amino acid in humans and is conditionally essential, i.e. under specific clinical conditions, including trauma and critical illness, endogenous synthesis is not sufficient to cover the needs. It is not included in standard parenteral mixtures since it is rapidly degraded. On the other hand, glutamine is the preferential substrate for rapidly growing cells, including epithelial and immune cells. These unique metabolic properties suggest a potential beneficial role of glutamine in cancer patients [21], and prompted the development of a specific pharmacological formulation of glutamine increasing its stability in solution. Intravenous glutamine is now available as a dipeptide and ongoing clinical trials will test its clinical efficacy in cancer patients [22]. Some concerns have been expressed regarding the possibility that glutamine may favour tumour growth via its synergic activity with glucose on glucose uptake and aerobic glycolysis [23]. Based on this evidence,

it is acknowledged that glutamine in cancer patients should be used cautiously, however, it must be also underlined that to our best knowledge, as yet no clinical study has been reported showing a proliferative-inducing effect of glutamine on human cancers.

When oral and EN are not sufficient or feasible, the use of PN in cancer patients with mild hypophagia and malnutrition at the beginning of their clinical journey, rather than at the very end when severe malnutrition and extreme fatigue have already developed, may protect metabolic and physical functions [24, 25]. Also, by intervening in an early phase of the clinical journey, patients will be more likely to also undergo a programme of mild physical exercise, whose anti-inflammatory properties are now well recognised [26].

Conclusion

PN has been considered of limited benefit in cancer patients, since many clinical trials have failed to report significant enhancement of clinical outcomes from the use of IV feeding predominantly based on glucose as the energy source. Increasing knowledge about the inflammatory pathogenesis of cancer cachexia and of the anti-inflammatory properties of specific nutrients has prompted the development of a new paradigm for the use of PN in cancer patients. The early start of IV feeding in mildly aphagic and malnourished cancer patients when oral intake or EN are not feasible or sufficient, even in conjunction with active antitumour treatment, is the mainstay of this new approach. More importantly, the fulfilment of the energy and protein needs by PN should be integrated by the infusion of anti-inflammatory nutrients to restore, at least in part, patients' metabolism and therefore the ability to fully utilise the infused nutrients, minimally influencing tumour proliferation rate.

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How radiotherapy can be used as a new approach in breast cancer

Professor Dr Günther J Wiedemann, PhD; Professor Dr Wolfgang Wagner, PhD

Best practice in adjuvant radiochemistry is gradually evolving. New techniques of administration offer localised and minimal-damage treatment, and many studies over several years are establishing an evidence base for timing and for which patients to treat.

It goes without saying that radiotherapy is not a new treatment of breast cancer. On the contrary, radiotherapy has been an important and integral component of treatment combinations in mammary carcinomas for decades. Adjuvant radiotherapy following breast-conserving resection of the tumour is a standard treatment because it reduces local recurrences of breast cancer and breast cancer mortality.

In the adjuvant situation, radiotherapy at a total dose of about 50 gray (Gy) will be given within five to six weeks, followed by a local boost (a top-up dose to the tumour bed itself with doses between 9 to 16 Gy).

Radiotherapy of the supraclavicular lymph pathways will be initiated when the number of lymph nodes (LNs) suspected of involvement is more than three. In this situation, the breast and the superior lymph pathways will be irradiated simultaneously.

After complete resection of the breast (mastectomy), however, radiation of the thoracic wall is only indicated when the primary tumour was larger than four centimetres in diameter and/or three or more involved LNs were found.

If used, adjuvant radiotherapy significantly decreases the number of in-breast recurrences after breast-conserving tumour resection and the number of local recurrences following mastectomy. Adjuvant radiotherapy reduces the recurrence rate from 30–40% to 10% (average decreases from 30–13%; see Figure 1) in both situations. More importantly, the overall survival rate is improved by 3.4% after five years and by 7.1% after 15 years (see Figure 1).

Surprisingly, the overall survival of breast cancer patients whose LNs are not involved (negative LNs), who have a comparatively good prognosis, is significantly improved after 15 years of follow-up (5.1%; see Figure 2).

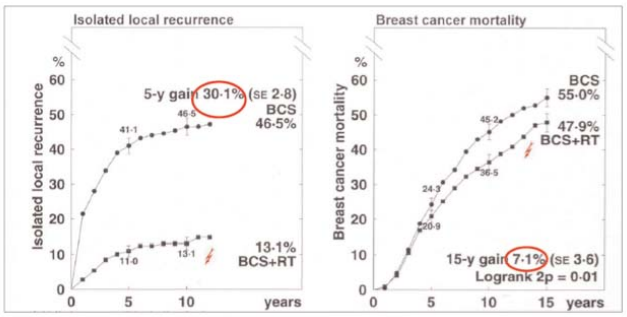
In the subgroup analysis of the 5-year risk of a local recurrence there is a strong correlation between age and outcome: young women (< 50 years) will profit most from using post-operative irradiation (see Figure 3). However, also elderly women gained an absolute benefit of 12% (see Figure 3).

The radiation boost (top-up dose of the tumour bed) is followed by a 50% decline in the risk of local recurrence independently of age after a follow-up of seven years (see Figure 4). Thus, the radiation boost is standard treatment. In patients with non-invasive breast cancer, mastectomy without adjuvant radiotherapy will cure the patients in most cases. The risk of local recurrence is up to 3%. After breast-conserving surgery, without adjuvant radiotherapy, however, the risk of local recurrence is unacceptably high (6–25%). Breast-conserving surgery is thus a clear indication for adjuvant radiotherapy (because the risk of local recurrence is lowered by 50%).

In breast cancer patients with small tumours (< 2 cm in diameter) and negative LNs, mastectomy alone is sufficient to cure the patients. In patients with positive LNs, however, mastectomy alone is not the treatment of choice. If mastectomy is combined with adjuvant radiation there is an overall survival benefit of about 10%. Even in the situation of involvement of a single LN adjuvant radiation effectively increases the overall survival by 10%.

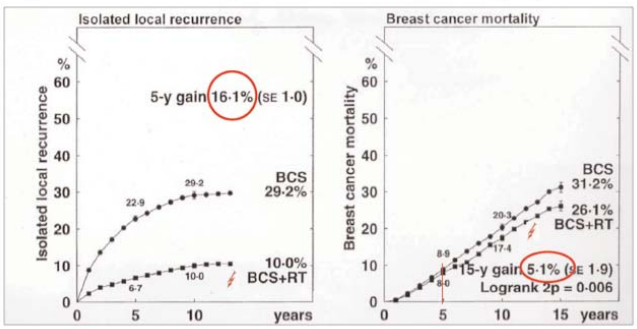
At the American Society for Radiation Oncology Conference

Figure 1: Benefit in patients with positive lymph nodes



After five years overall survival improvement of 3.4%, after 15 years (7.1%)

Figure 2: Benefit in patients with negative lymph nodes



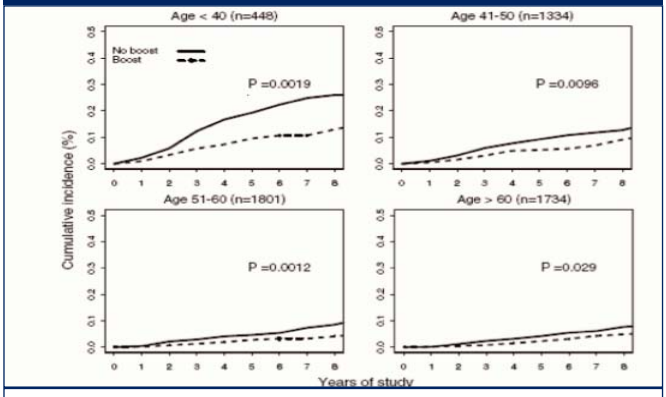
After five years no improvement in overall survival, after 15 years 5.1%

Figure 3: Subgroup analysis: LRR and age EBCTCG 2005

Characteristics (where known*)	5-year local recurrence risk (%) in trials of: (a) BCS ± RT node-negative		(b) Mast+AC ± RT node-positive	
	Radiotherapy vs control	Absolute reduction (SE)	Radiotherapy vs control	Absolute reduction (SE)
Age (years)				
< 50	11 vs 33	22 (2)	6 vs 23	17 (1)
50 – 59	7 vs 23	16 (2)	6 vs 24	18 (2)
60 – 69	4 vs 16	12 (1)	5 vs 23	18 (2)
70+	3 vs 13	11 (2)	-	-

correlation between age + outcome
young women will profit mostly
elderly women gain 12% absolutely
after mastectomy, no influence of age
EBCTCG: early breast cancer trialists' collaborative group.

Figure 4: Outcome after boost is independent from age



Radiotherapy will decrease risk rate by about 50% seven years after therapy
EORTC 22881-10882. Antonini N, et al. Radiother Oncol. 2007;82:265.

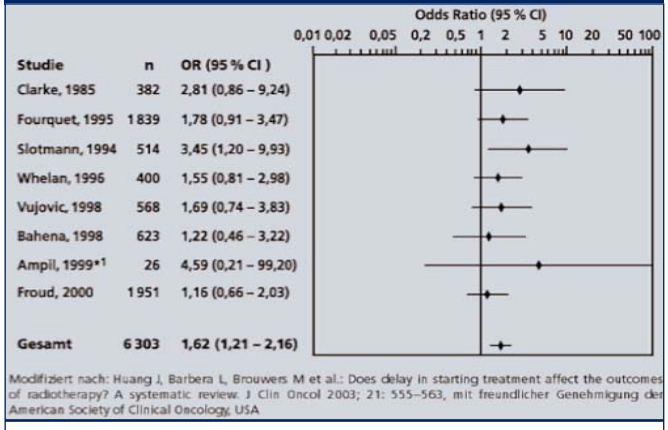
in Chicago, USA, October 2008, Dr Romestaing and co-workers presented the results of the phase III study concerning the value of irradiation of the mammaria interna lymph pathway after mastectomy. This study found there was no difference in survival after irradiation of the lymph pathway or no treatment. Concerning subgroup analysis there was no difference between histological subtypes, no difference between external versus internal tumour localisation and no difference concerning involved or non-involved axillary LNs.

There is one crucial effect compromising the benefit of irradiation and this is time between surgery and irradiation. In patients with risk factors chemotherapy has to be interposed and this will mean that irradiation will start months after the end of surgery and this is a negative prognostic factor.

Clearly, radiation therapy which starts months after surgery (which is at present the normal situation in Europe) is a negative prognostic factor (see Table 1).

As demonstrated in Table 1, local recurrence rates will rise when the time interval between surgery and radiation is more than eight weeks, which is a problem due to the primacy of adjuvant chemotherapy. This problem can be solved by accelerated partial breast irradiation (APBI).

Table 1: Time between surgery and start of irradiation



Modifiziert nach: Huang J, Barbera L, Brouwers M et al.: Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003; 21: 555–563, mit freundlicher Genehmigung der American Society of Clinical Oncology, USA

Recurrence rate increases when time interval is more than eight weeks.
Primacy of chemotherapy.

APBI is defined as irradiation therapy after breast-conserving surgery to the tumour bed plus a margin of one to two centimetres around the tumour. The total treatment time of irradiation is one week or less. Today, different techniques of APBI have been developed, e.g. a balloon catheter technique (MammoSite), multicatheter techniques or intraoperative radiotherapy with fast electrons or intrabeam treatments.

At present, only elderly breast cancer patients after complete resection of small tumours with negative LNs and a positive hormone receptor status have been treated (these patients will have a good prognosis without adjuvant treatment). Definite results are expected in 2015. Preliminary results are encouraging: the acute undesired treatment effects are mild and the local recurrence rate is very small.

Literature can be requested from the authors.

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Different demands, common understanding: the roles of physicians and pharmacists

Chemotherapy patients are cared for by a multidisciplinary team. Although tasks and responsibilities are allocated differently between doctor and pharmacist in different countries, there is much agreement that a patient-centred model of care offers many advantages.

The comprehensive care of patients who are undergoing chemotherapy is always setting new challenges. Therapies are becoming ever more complex as the cost of care rises. One of the challenges is to make the best use of scarce staff resources and one way is to optimise communications and cooperative structures in a multidisciplinary team.

Ralf Klask MD

Goentje-Gesine Marquardt

A discussion on the distribution of tasks between doctors and pharmacist was held at the 2010 ESOP meeting in Hamburg, Germany. The goals of one of the plenary sessions were to scan current multidisciplinary oncology practice across Europe and recommend improvements where appropriate.

There are clear divisions of care in many countries. Making the diagnosis, staging, choosing the chemotherapy and first investigation of the patient were clearly defined by all participants as part of a doctor's domain. The preparation of cytotoxic drugs, checking the dosages including the cumulative dose as well as the documentation, was on the other hand unanimously declared to be the work of pharmacists.

However there was intense discussion on the division of tasks in grey areas such as dose changes, control of adverse effects, supportive care including nutrition as well as the guidance and encouragement of patients undergoing cancer treatment. In most countries the doctor has the responsibility and leading role in these grey areas. The pharmacist stands to the side in an advisory and checking capacity.

Our opinion is that if the doctor is the bridge between patient and pharmacist a lot of potential is lost, because the doctor functions not only as a bridge but also as a filter. Their decisions are not sufficiently challenged and the areas of supportive care and nutrition are usually neglected.

The best patient care demands joint care of the patients in the grey areas. More regular personal contact between patients and the pharmacist or clinical pharmacologist brings much additional information to both. The pharmacist can make direct use of his/her expertise in pharmacotherapy, recognition and treatment of side effects and particularly in supportive care. Our experience indicates that more information about incompatibilities and side effects is revealed, and earlier, in conversations between patients and the pharmacist. Patients generally feel a pharmacist is less intimidating and are less anxious about revealing problems. They are reluctant to mention these to a doctor for fear of the treatment being discontinued or reduced.

Figure 1: The dialogue and tasks overlap in a patient-centred model of care

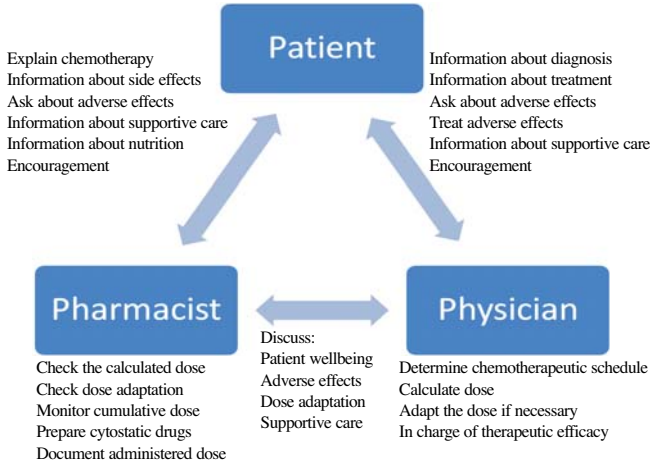

Table 1: Responsibilities for different tasks in patient care: conclusions of the meeting

Task	Physicians	Pharmacists	Other help
Diagnosis, therapeutic plan	x		
Information about chemotherapy	x		
Dose calculations	x	x (control)	
Dose adaptation	x	x	
Preparation		x	
Documentation of the administered dose		x	Computer/ Nurse
Adverse effects	x		
Information about supportive care		x	
Information about special diet		x	Dietician
Encouragement	x	x	

When the pharmacist has an insight into the patient's current situation he/she is better placed to make suggestions in the area of dose changes, adverse effects and supportive care. Bringing together all the information through good communication between doctor and pharmacist is important. The final responsibility for dose changes and the treatment remains with the doctor.

The discussion indicated that regular patient-pharmacist contact only belongs to the care concept in a few centres. The main reason was thought to be the lack of clinical pharmacologists. Many countries require qualification as a clinical pharmacologist before pharmacists are legally allowed to practice this kind of patient care.

An important element in the communication between doctor and pharmacist is the computer system. There was consensus that in the area of dose calculation and changes a check of the doctor's prescription by the pharmacist is a priority. This is best done with computer support. A heated debate took place over the type of dose calculation (Body Surface Area) and dose banding. While dose banding is used in Denmark and UK, in the absence of studies other countries continue to calculate and use exact doses.

Summary

The discussion revealed considerable differences in the division of tasks between doctor and pharmacist in the care of chemotherapy patients. Everyone considered regular personal pharmacist–patient contact worthwhile in addition to regular doctor–patient contact. But this is not achieved for a variety of reasons in most countries or is not possible for legal reasons.

We suggest that our model for joint direct patient care offers a clear improvement and the possibility of more efficient ways of working. A precondition for this is good communication between doctor and pharmacist.

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2010 ASCO Annual Meeting: progress in difficult-to-treat cancers

The 46th Annual Meeting of the American Society of Clinical Oncology took place in June 2010 in Chicago, USA. More than 30,000 specialists discussed the latest innovations in research, quality, practice and technology in cancer. Here we highlight the most significant advances in difficult-to-treat cancers [2].

Important positive trials

Advanced/metastatic non-small-cell lung cancer

In 2007, Soda et al. described the identification of the EML4-ALK fusion gene in *Nature* [1]. When the ALK gene fuses with the EML4 gene, it promotes lung cancer cell growth by encoding the production of a tumour-specific protein called anaplastic lymphoma kinase, or ALK—an enzyme that is critical for the growth and development of cancer cells. In 2010, only three years later, a clinical trial supported the concept of molecular selection of lung cancer patients for appropriately-designed treatment. The ALK inhibitor **crizotinib** (Pfizer-02341066), which is taken orally, works by inhibiting the ALK enzyme, shows high response rates in patients with advanced ALK-positive non-small cell lung cancer who had received three or more prior standard treatments. An expanded phase I clinical trial found that the large majority (approximately 90%) of these patients responded to treatment with the investigational oral ALK inhibitor, and the objective response rate, which is the rate of CR and PR, was 57%. The responses were durable (up to 15 months) and a 72% probability of being progression-free at six months was found. Gastrointestinal toxicities, including nausea and vomiting were the most frequent adverse events (Bang et al. Abstract # 3).

Professor Günther J Wiedemann, MD, PhD

Professor Wolfgang Wagner, MD, PhD

The drug combination of monthly **carboplatin** (AUC 6) and weekly **paclitaxel** (90 mg/m^2) prolonged survival in patients aged 70 to 89 years compared to the standard single-agent therapy of **gemcitabin**e (1150 mg/m^2, weekly) or **vinorelbine** (30 mg/m^2, d1+d8). Overall survival was longer in the drug combination group (10.4 months) than in those who received single-agent therapy (6.2 months). The researchers found that patients receiving combination therapy lived nearly twice as long before their lung cancer progressed (6.3 months) as those receiving the single-drug therapy (3.2 months). While the researchers found the combination therapy had acceptable toxicity, preliminary data in 313 elderly patients found that the group receiving the combination regimen experienced moderate to severe neutropenia more frequently than the single-agent group (Quoix et al. Abstract # 2).

Inoperable advanced and metastatic malignant melanoma (stage III and IV)

Therapy with **ipilimumab** (90 min infusion every three weeks for four doses) – a monoclonal antibody directed against CTLA-4 on the surface of T lymphocytes – in patients with metastatic malignant melanoma lengthens survival significantly (four months difference) in a large phase III trial. Ipilimumab can overstimulate the immune system leading to attack of T lymphocytes on normal skin and skin cancer, because CTLA-4 is blocked. CTLA-4 serves as a control switch for the immune system's response. Blocking CTLA-4 accelerates/potentiates the T lymphocytes resulting in attack and death of cancer cells. With no ipilimumab-antibody attached, CTLA-4 suppresses the immune response. In a large phase III (676 patients), randomised, double-blind, multicentre study (125 centres, 13 countries) comparing monotherapy with ipilimumab versus gp100 peptide vaccine versus the combination, ipilimumab was found to improve overall survival. Ten to 15% of ipilimumab immune side effects were severe and required immunosuppressive therapy (steroids) (O'Day et al. Abstract # 4).

Advanced ovarian cancer (stage III or IV)

Bevacizumab prolongs progression-free survival for patients with advanced ovarian cancer (median of 14.1 months versus 10.3 months) when combined with the standard chemotherapy (six cycles of **carboplatin** AUC 6 combined with **paclitaxel** 175 mg/m^2) and maintained for 10 months (15 mg/kg b.w.). The combination of the standard chemotherapy with bevacizumab without 10-months bevacizumab-maintenance therapy (infusions at d1 of a 21d cycle) does not however improve survival. Patients experienced bevacizumab-associated undesired treatment effects (primarily hypertension and low white blood cell counts), the types and frequency appeared to be similar to what has been reported previously (Burger et al. Abstract # LBA1).

Advanced prostate cancer

Adding radiation therapy (65-69 Gy; frx: 1.8-2 Gy, photon therapy to the whole pelvis plus boost to the target organ) to continuous hormonal therapy improves survival in men with locally advanced prostate cancer. Adding radiation therapy to hormone therapy decreases the risk of dying from prostate cancer by 43% in men with locally advanced or high risk prostate cancer (PSA > 20, Gleason > 8, T2c-T4) with no significant increase in late treatment toxicity (deaths after a 6-

year-follow-up: hormone therapy alone: 175/602, radiation plus hormone therapy: 145/603) (Warde et al. Abstract # CRA4504).

Metastatic breast cancer

Eribulin (Eisai7389), a nontaxane microtubule dynamics inhibitor that affects cell division, increases survival among women with metastatic breast cancer. An international, multi-centre phase III trial, called EMBRACE, found that eribulin mesylate (1.4 mg/m^2) 2-5 min IV bolus on days 1 and 8 of a 21-day-cycle), extends median overall survival by 2.5 months among women with metastatic breast cancer who had already been heavily treated with an average of four prior conventional cytotoxic drugs (including an anthracycline and a taxane). Because no single chemotherapy regimen is standard for these women, physicians chose which treatment to give patients in this study's control arm, to reflect real-life choices. The median survival for the eribulin group was significantly longer: 13.1 months versus 10.7 months. The study's secondary endpoints (progression-free survival and objective response rate) also favoured eribulin, which was generally well tolerated. EMBRACE is the first single-agent study in heavily pre-treated metastatic breast cancer to show improved overall survival (Twelves et al. Abstract # 504).

Important negative trials

Resected stage III colon cancer with normal *KRAS*

Adding **cetuximab** (Erbitux) to standard adjuvant FOLFOX-chemotherapy in patients with resected stage III colon cancer (T1-4, N1-3, M0) and normal *KRAS* gene activity does not prolong their lives, and is associated with significantly more side effects. This large (n = 1760), randomised, phase III trial, which was terminated early due to the results, showed clearly that the combined treatment with cetuximab should not be used in patients with resected stage III colon cancer (Alberts et al. Abstract # CRA3507).

Resected stage I (IA and IB) non-small-cell lung cancer

Selenium (200 μgm/d) does not prevent second lung cancer. On the contrary, the selenium group had approximately 5% lower survival at three and five years. In this randomised, double-blind, phase III trial (selenium versus placebo) compliance was excellent (pill count/phone interview data first two years), diabetes risk and risk of non-melanoma skin cancer were not increased. Overall, approximately 4.1% of participants who took selenium developed a second primary tumour of any type after one year, compared to 3.66% in the placebo group. Side effects were minimal (Karp et al. Abstract # CRA7004).

News in clinical oncology in breast cancer

Removing additional axillary lymph nodes to look for more breast cancer cells in women with limited disease spread in the sentinel node does not improve survival, according to results from a phase III study. Up to now, axillary lymph node removal has been the standard approach for women with micro- and macro-metastases in the sentinel node. The findings suggest that there may not be a benefit to removing more lymph nodes than the sentinel node only, and that women can avoid the risk of additional side effects that come with more extensive lymph node removal (Giuliano et al. Abstract # CRA506).

Primary breast cancer tumours that spread to the liver may change tumour biology, impacting treatment effectiveness, requiring a change in therapy in more than 12% of patients. In this study, researchers examined biopsy data from primary breast cancer tumours and liver metastases in 255 women with metastatic breast cancer to determine the status of oestrogen and progesterone receptors and HER2. They found changes in oestrogen receptor status in the metastases in 14.5%, progesterone receptor status in 48.5%, and HER2 receptor status in 13.9% of cases (Locatelli et al. Abstract # CRA1008).

Using immunohistochemistry testing to identify breast cancer micrometastases in the sentinel node and bone marrow does not help predict survival. A large observational trial of more than 5,500 women with early-stage breast cancer (T1/T2 N0 M0) who had breast-sparing surgery (lumpectomy) showed that using immunohistochemistry to detect occult micrometastases in sentinel lymph nodes and bone marrow does not predict overall survival and should not be used to guide treatment decisions (Cote et al. Abstract # CRA504).

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2. www.asco.org/ASCOv2/Meetings/Abstracts [Accessed 27 July 2010].