Editorial

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Sustainability in health care – changing mind, knowledge and behaviour

Klaus Meier
Editor-in-Chief

EJOP

'If the shipbuilders are the uncles of the sailors, the ship will not sink. When people, however, produce goods for foreigners, the quality becomes a problem.' Marvin Harris

Besides these words from anthropologist Mr Marvin Harris, who espoused a number of controversial theories about the evolution of human cultures, the human understanding about behaviour change seems poor.

Throughout human history, the sociocultural systems adapt to new environments using new technologies and practices in the infrastructure. Many people before and after Harris declared this as crucial to the survival of individuals and sociocultural systems. The adoption of new technologies can have tremendous impact on human institutions and cultural values and beliefs, as stated by Ms Myrna Oliver in *The Washington Post* in October 2001.

Relationships between producers and customers can be realised through an affinity between patients and healthcare professionals. As we learn to understand ourselves better as part of society and reflect that everything we do has an influence on others and an impact on the future, this is why we focus our work on sustainability. As we learn to understand ourselves, we will become increasingly familiar with sociocultural systems in different parts of the world through daily use of modern technologies.

Oncology pharmacists do not operate in isolation to serve patients as the treatment affects the entire personality. Multiprofessional teams are key to a good outcome. Patients nowadays do not want mere words, they increasingly wish to become involved in creating treatment guidelines. We know that participation in decision-making processes increases concordance, and that being patronising towards self-conscious individuals does not bring patient satisfaction. Both pharmacists and oncology physicians are learning to form multiprofessional teams.

The important meeting of European CanCer Organisation (ECCO) member societies held in May 2012 in Brussels, Belgium, had the purpose of discussing ways of increasing harmony and structure in the development of European multidisciplinary and multi-professional guidelines, in order to increase quality and use of European guidelines.

Representatives from ECCO Societies revealed that, indeed, all together, a significant amount of work is devoted by the ECCO member societies to guidelines, on a variety of activities, variable for each society.

More than 12 years ago, ESOP began to establish understanding about the role of pharmacists in oncology and in patient care. Recognising the progress of treatment and the increasing number of cancer patients with chronic disease, we need to improve our understanding about the pharmacy profession and the demands of patients in order to guarantee good quality treatment.

Now in its sixth year, EJOP exists to support this goal. In addition to reports about new treatment or regimens for breast cancer or oesophageal carcinoma, for example, we feature also pharmacological prevention of cancer, the role of the pharmacist in oral antineoplastic drugs, the importance of correct order, time and frequency of combination chemotherapy as a representation of the vastly increased knowledge that now exists in the oncology field.

Reading the latest edition of EJOP and participating in the great European Conference of Oncology Pharmacy, in September 2012, Budapest, Hungary, I hope will provide you with a strong starting point for empathising with progress and advancing the need for sharing knowledge.

EJOP is an active member of Directory of Open Access Journals

The *European Journal of Oncology Pharmacy* (EJOP) is an active member of the Directory of Open Access Journals (DOAJ). As such, we are pleased to announce that from 2011 DOAJ has partnered with the European Commission's IST-PSP funded programme – Europeana Libraries.

What does this mean for you as a subscriber to EJOP? Besides already having access to EJOP's electronic articles on the EJOP website (www.ejop.eu) and on DOAJ, you will also be able to view our electronic articles on the European Library and Europeana websites where five million digital objects (articles, books, figures, images, etc.) from 19 leading European research libraries are being put online and made searchable.

EJOP's articles, which provide information on professional topics to practising oncology pharmacists and technicians, will be amongst the five million digital objects to be included in this project.

To learn more about this project that EJOP is involved in, please visit the European Library homepage on the project website: http://www.version1.europeana.eu/web/europeana-libraries.

New rules in the oncologic therapy of oesophageal carcinoma

The outlook for adenocarcinoma and squamous cell cancer of the oesophagus has improved recently. This article reviews the use of surgery, radiotherapy and chemotherapy in different combinations, and palliative treatment, depending on the stage of disease, and the expression of molecular markers.

The past two decades have seen dramatic changes in the incidence and therapy of most tumour types, particularly a drop in the incidence of lung cancer and colorectal carcinoma. Meanwhile certain other tumours are becoming more prevalent, for instance adenocarcinoma of the oesophagus, see Figure 1. This trend is a cause for concern, particularly given the relatively poor prognosis for advanced cases of this type of cancer. Until recently treatment options were limited, but new approaches are now being explored which have potential to improve survival.

Professor Günther J Wiedemann, MD, PhD — Professor Wolfgang Wagner, MD, PhD

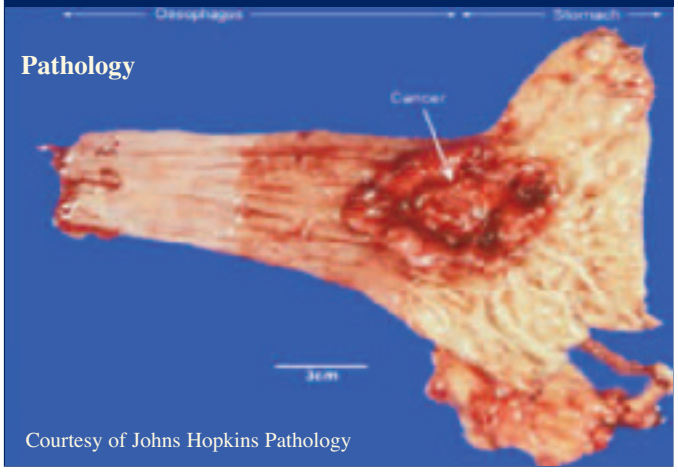
Figure 2 shows the ascending incidence of oesophageal adenocarcinoma since the 1970s in both men and women [1]. This increase is likely to be related to lifestyle: obesity, reflux symptoms and Barrett's oesophagus [2] are already well-known risk factors, see Table 1. The classical therapy for this tumour is surgery. Surgery provides acceptable 5-year survival rates for early-stage cancers, see Table 2, but in more advanced cancers the survival rate drops to 20%. Hence, only a limited number of cases benefit from surgery. There is no difference in outcome between results from hospitals with high-volume versus low-volume throughput of patients (perioperative mortality and the 1-, 3- and 5-year overall survival rates).

Regarding the surgical route, for a long time it was unclear whether a transthoracic operation or transhiatal surgery was superior. Hulscher et al. [3] reported in the *New England Journal of Medicine* in 2002 that the transthoracic approach provided a trend towards a better survival whereas the transhiatal approach shows lower morbidity. For more advanced tumour stages, investigators have tried to improve results using preoperative chemotherapy. A meta-analysis of 685 papers containing the results of preoperative chemotherapy revealed a 2-year survival benefit of just 6–9% for oesophageal adenocarcinoma. A complete pathological response was seen in only 2–5% of all patients [4]. Therefore we can assume that the classic preoperative chemotherapy has little benefit for most patients, especially for the subgroup of squamous cell carcinomas.

What is the benefit of irradiation?

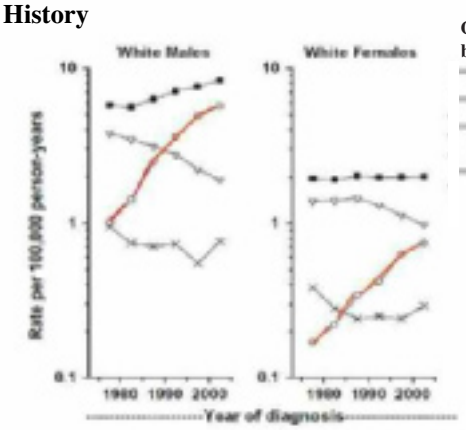
Until end of the 1980s the benefit of irradiation was unclear. Studies tended to be sub-optimally designed, underpowered and using relatively old cobalt-60 gamma ray-based technology. However, the potential of radiotherapy in the treatment of oesophageal adenocarcinoma is becoming clearer. With three large investigations the Radiation Therapy Oncology Group (RTOG) has defined what radiation can achieve. Herskovic et al. found that radiotherapy alone is less effective than combined radio- and chemotherapy, using a total dose of 50.4 Gy together with concurrent administration of 5FU and Cisplatin (cisdiamminedichloroplatinum(II)). The combined arm of the trial showed significantly improved median and overall survival rates [5].

Figure 1: Adenocarcinoma of the gastro-oesophageal junction



Courtesy of Johns Hopkins Pathology

Figure 2: Rising incidence of the adenocarcinomas



Brown LM et al. J Natl Cancer Inst. 2008

Table 1: Risk factors for oesophageal cancer* (adenocarcinoma and squamous cell carcinoma)

Risk Factors	Squamous cell carcinoma	Adeno-carcinoma
Tobacco use	+++	++
Alcohol use	+++	---
Barrett's oesophagus	---	++++
Weekly reflux symptoms	---	+++
Obesity	---	++
Poverty	++	---
Achalasia	+++	---
Caustic injury to the oesophagus	++++	---
Non-epidermolytic palmoplantar keratoderma (tylosis)	++++	---
Plummer-Vinson syndrome	++++	---
History of head and neck cancer	++++	---
History of breast cancer treated with radiotherapy	+++	+++
Frequent consumption of extremely hot beverages	+	---
Prior use of beta-blockers, anti-cholinergic agents, or amino-phyllines	---	±

*A single plus sign indicates an increase in the risk by a factor of less than two, two plus signs an increase by a factor of two to four, three plus signs an increase by a factor of more than four to eight, and four plus signs an increase by a factor of more than eight. The plus-minus sign indicates that conflicting results have been reported, and the dashes indicate that there is no proven risk.
Enzinger PC et al. NEJM. 2003

Table 2: Stage grouping and survival concerning surgery

Stage		5-year Survival
Stage 0	TisN0M0	
Stage I	T1N0M0	80–90%
Stage IIA	T2-3N0M0	50%
Stage IIB	T1-2N1M0	20%
Stage III	T3N1/T4N0-1M0	10–15%
Stage IVA	M1a	10%
Stage IVB	M1b	Anecdotal

Source: ASTRO 2010

The 5-year survival rate in this combined radiochemotherapy group was 20–30%, which is in the range of surgery alone. However, there was a high-local failure rate in about 40–50% in patients who did not receive surgery. Other researchers have tried to improve the results with a higher radiation dose. An attempt to raise the dose to more than 64 Gy met with disappointment: the total local failure rate and overall survival time were identical in both arms, and showed more toxicity in the high dose arm [6].

Table 3: Oesophageal cancer–preoperative radiochemotherapy phase III trials

Study	Path	Regimen	# pts	Path CR
Urba (Michigan, USA)	SCC+ Adeno	FU-CDDP-Vinb/45Gy Surg	60 50	28 -
Bosset EORTC	SCC	CDDP/37 Gy Surg	143 138	20 -
Walsh (Ireland)	Adeno	FU-CDDP/35 Gy Surg	58 55	22 -
Burmeister (Australia)	SCC+ Adeno	FU-CDDP/35 Gy Surg	128 128	16 -

Currently, studies are underway to explore whether outcomes can be improved with new chemotherapy agents such as anthracycline, cetuximab, erlotinib and taxane. The prospects for using neoadjuvant radiochemotherapy (to shrink the tumour prior to surgery) were unclear up to the end of the 1990s. Four randomised studies, see Table 3, demonstrated complete pathological responses in 16–28% of patients who had received neoadjuvant radiochemotherapy compared to only 2–5% of those receiving chemotherapy alone [7-10]. However, only two studies showed improvement in overall survival.

More recent studies have shown considerable benefit for adenocarcinoma patients given combined radiochemotherapy. The Preoperative Oesophageal Therapy (POET) study, for example, was a phase III study in Germany which included T3/T4 oesophagogastric adenocarcinomas, these patients were randomised to receive either chemotherapy and surgery or radiochemotherapy and surgery [11]. The study was closed early because of poor patient recruitment. Nevertheless overall survival for the combined irradiation/chemotherapy group was superior. In the meantime, Tepper et al. showed that combined radio- and chemotherapy before surgery for advanced adenocarcinoma significantly improves both median and 5-year survival rates [12].

With regard to advanced cases of squamous cell carcinoma of the oesophagus, Bedenne et al. treated 444 operable patients (89% squamous cell carcinomas) with two courses of combined radiotherapy with 5FU+CDDP and randomised just those patients who responded to chemotherapy to receive either surgery or just further chemoradiation [13]. Results were the same in both groups. Hence, trimodality treatment (radiochemotherapy followed by surgery) is not generally recommended and does not further enhance survival in squamous cell carcinomas. We now know that only those patients who did not respond to radiochemotherapy will gain benefit from surgery.

Nevertheless, we must keep in mind the high recurrence rate of 40–50% in the non-surgical group. The RTOG has begun a

phase II study with induction chemotherapy—Paclitaxel, 5FU and platin, followed by irradiation. Surgery is reserved as a salvage therapy only.

What are the benefits of post-operative irradiation for squamous cell carcinoma of the oesophagus?

Fok et al. reported that while post-operative radiotherapy may improve local control in patients whose surgery achieved complete tumour resection (R0), its associated toxicity results in worse overall survival, for patients with squamous carcinomas [14]. Another study which randomised 549 patients with squamous cell carcinoma of the oesophagus between surgery alone and post-operative irradiation, showed that post-operative radiotherapy significantly decreased the local recurrence failure in all patients and was able to improve survival only in patients with lymph node-positive tumours [15].

According to ESMO 2010 Guidelines, surgery is the only treatment of choice for early squamous cell carcinoma. For patients who are unable or unwilling to undergo surgery, combined radiochemotherapy is a viable treatment alternative and is superior to radiotherapy alone [16].

In summary, with regard to extensive disease, surgery alone is no longer a standard treatment option. We must differentiate between squamous cell carcinomas and adenocarcinomas. In patients with squamous cell carcinoma, preoperative radiochemotherapy, or definitive radiochemotherapy have become the standard first line of treatment. Surgery should only be used as salvage treatment for those patients who fail to respond.

In patients with adenocarcinoma, neoadjuvant chemotherapy with 5FU+CDDP is now standard before surgery, particularly following recent phase III studies demonstrating radiochemotherapy as an alternative to chemotherapy alone. The recent meta-analysis [16] reveals a significant survival benefit for adenocarcinomas, especially in high-risk patients.

Finally, in patients with metastases, brachytherapy gives superior results in comparison with stent application, with better relief of dysphagia and fewer complications. Chemotherapy should include new substances besides only 5FU+CDDP. Furthermore, the *HER2*/neu status of adenocarcinoma of the gastro-oesophageal junction should also be measured. If this marker is found to be overexpressed, then therapy with trastuzumab should also be considered.

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Pharmacological prevention of cancer

Some risk factors for cancer like obesity, sedentary lifestyle, smoking, diabetes or alcohol abuse are modifiable by lifestyle interventions. In individuals highly at risk, chemoprevention may be considered after evaluation of the risks and benefits.

Professor Dr med Günther J Wiedemann, MD, PhD

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Facing the still growing incidence of cancer worldwide, there has been emerging interest in chemoprevention of cancer. Primary prevention means preventing cancer in healthy individuals (at high risk); secondary prevention is preventing premalignant conditions from becoming cancer such as polyps as precursors of colorectal carcinomas or oral premalignant lesions as precursors of head and neck cancer; tertiary prevention is preventing recurrences or secondary cancers in patients after cancer treatment. Some substances have already proven to be effective in preventing breast cancer, e.g. tamoxifen, raloxifene [1, 2]; colorectal adenomas, e.g. aspirin and COX-2 inhibitors [3-5] and prostate cancer, e.g. finasteride [6]. Others, like antidiabetics, vitamin D, or statins cannot be considered as established chemopreventive agents. Given the risk of adverse effects of any medication, primary chemoprevention, which means treatment of healthy subjects at only statistically elevated cancer risk, needs to be discussed carefully with patients considering risks and benefits in a shared decision-making process to avoid unnecessary toxic effects and non-adherence.

Tamoxifen, raloxifene and aromatase inhibitors for breast cancer prevention

Tamoxifen is suitable for chemoprevention in both pre- and postmenopausal women, raloxifene in postmenopausal women with decreased bone density. Tamoxifen (20 mg/d for five years) was shown to reduce breast cancer risk for women at high risk (Gail score at least 1.7%, visit www.cancer. gov/bcrisktool) by 49% [1]. Other studies could not confirm this strong preventive effect of tamoxifen [7, 8]. Tamoxifen covers all three prevention settings, primary prevention in healthy women at high breast cancer risk, secondary prevention in ductal carcinoma *in situ* and tertiary prevention of contralateral breast cancer. Major side effects are hot flushes, vaginal dryness, endometrial cancer, cataracts and thromboembolic events such as pulmonary embolism and strokes.

Raloxifene seems to be not quite as effective as tamoxifen in reducing the risk of invasive breast cancer [2]. It markedly decreases the risk of oestrogen receptor-positive tumours–relative risk (RR) 0.10 [9], but not the risk of hormone receptor negative tumours–RR 0.88. As it leads to considerably less endometrial stimulation, women who still have their uterus might prefer raloxifene. Side effects of raloxifene are hot flushes, influenza-like syndromes, thromboembolic events and peripheral oedemas. Raloxifene has positive effects on bone density.

Contraindications to tamoxifen or raloxifene include a history of deep vein thrombosis, pulmonary embolus, thrombotic stroke and transient ischaemic attacks. The risk–benefit ratio is influenced by age, various comorbidities and presence of uterus. Until now, only limited data are available for tamoxifen and raloxifene use for > 5 years. Women taking preventive tamoxifen and raloxifen need continued yearly mammography due to their increased cancer risk.

Given the effectiveness of aromatase inhibitors– anastrozole, letrozole, exemestane–in the adjuvant setting of breast cancer therapy it is likely that they can play a role in primary prevention as well. A recent study [10] showed a 65% relative reduction in the annual incidence of invasive breast cancer with exemestane. The risk–benefit ratio may be more favourable than with tamoxifen or raloxifene, as adverse events–bone fractures, cardiovascular events, other cancers, treatment related deaths–occurred in 88% as compared with 85% in the placebo group. Aromatase inhibitors raise the risk of osteoporosis, common side effects include hot flushes, joint and muscle pain, headache and fatigue.

Finasteride and other 5-alpha reductase inhibitors (5-ARIs)

5-alpha reductase inhibitors reduce the level of dihydrotestosterone, a promoter of prostate cancer. Finasteride can lower prostate cancer risk by 25% [11]. Although there remain uncertainties regarding the risk–benefit ratio, American Society of Clinical Oncology and American Urological Association released in 2008 guidelines on the use of 5-ARIs for reducing prostate cancer risk in men undergoing regular prostate-specific antigen screening.

Statins

Statins may inhibit tumour initiation, growth and metastasis. Preclinical results showed antiproliferative, proapoptotic and anti-invasive properties of these agents. A decrease in overall risk of cancer shown in observational studies could though not

be confirmed by meta-analyses of randomised trials [12, 13]. Further investigations are needed to prove or disprove anti-cancer properties of statins.

Hypoglycemic agents (thiazolidinediones [TZDs], metformin)

High insulin levels are associated with a higher overall cancer risk, leading to a strong correlation of type 2 diabetes and cancer. This is due to the anabolic effect of insulin with stimulation of DNA synthesis and cell proliferation and the cross-activation of the insulin-like growth factor receptor family. It is plausible that a reduction of insulin levels, be it by means of physical activity, weight reduction or therapeutic agents, can reduce cancer risk.

Metformin inhibits the growth of cancer cells [14]. It may be effective in primary cancer prevention in diabetic patients—31% reduction in cancer risk [15], as well as in tertiary prevention in the adjuvant setting [16].

TZDs are acting on a nuclear receptor which has a role in cell cycle arrest; this might inhibit cell proliferation. In a retrospective cohort study there was a 26% relative decrease in lung cancer in diabetics treated with TZDs as compared with controls treated with other antidiabetics [17]; the study had methodological limitations, e.g. the smoking status in the treatment and control arm was not known.

Non-steroidal anti-inflammatory drugs (NSAIDs)

COX-2 and prostaglandines are overexpressed in carcinogenesis and can be suppressed by NSAIDs. Celecoxib is FDA approved for patients with familial adenomatous polyposis who carry a 100% risk of colorectal cancer, 400 mg celecoxib twice daily for six months reduced the polyp burden by 31% [18]. The relatively short intervention raises the question what happens if the underlying genetic alteration persists in some cell clones after chemopreventive therapy. Chemoprevention may actually delay rather than prevent cancer, such offering more healthy years to patients at high cancer risk. Aspirin may be effective in tertiary prevention of breast cancer, as aspirin intake is related with a decreased risk of recurrence and breast cancer related death–RR for breast cancer death 0.29 with 2–5 aspirin intakes per week [19]. The studies regarding effects of NSAIDs like aspirin in primary prevention of cancer are contradictory. Considering the relatively high risk of major gastrointestinal bleeding, aspirin use with preventive intention cannot be recommended for the general population.

Supplements as selenium, vitamin E and D

Neither selenium nor vitamin E reduced prostate cancer risk in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [20]. Women who take multivitamins do not reduce their risk of getting breast, colorectal, endometrial, lung or ovarian cancers [21]. Vitamin D seems to be a more promising candidate for primary prevention, but more evidence is needed [22].

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The importance of correct order, time and frequency of combination chemotherapy

The chronology of which drugs to give in chemotherapy combination regimens is critical to their effectiveness. A cytotoxic drug can become antagonistic if used in the wrong sequence with other agents. This article outlines those combination chemotherapies in which the order of drug administration is most relevant.

Chronology of combination chemotherapy

The first effective drugs against cancer were used in the mid-1940s. The initial (mono-) therapeutic results were disappointing. Only partial remissions of short duration were achieved. A landmark of antineoplastic therapy was the introduction of combination chemotherapy approximately 10 years later against childhood acute lymphoblastic leukaemia.

Jürgen Barth

The concept of combination chemotherapy was to take advantage of synergistic, additive, or over-additive pharmacological antitumoural effects of different substances. At the same time, overlapping organ toxicities were to be avoided where possible. The initial strategy was first to give a mitosis inhibitor, such as a vinca alkaloid, to synchronise all dividing cells, including the tumour cells, into the S phase of the cell cycle. This was followed by phase unselective agents such as alkylating drugs; or phase dependent drugs, for example, antimetabolites; but the approach turned out to be 'bath tub pharmacology' and did not succeed. The drugs failed to distribute uniformly or to have the same speed of action throughout the body. Patients showed pharmacokinetic, biochemical and pharmacogenetic differences. Subsequent observations revealed, however, that there were agonistic as well as antagonistic drug interactions depending on the chronological order of their administration.

Examples of drug interactions in combination chemotherapy include:

- Methotrexate (MTX) before 5FU boosts the activation of 5FU (see old breast cancer scheme CMF = Cyclophosphamide → MTX → 5FU)
- MTX before Cytarabine (= Ara C) boosts the activation of Cytarabine
- Folate enforces the inhibition of thymidylatesynthetase by 5FU if given before or together with 5FU [1, 2]
- Inhibitors of pyrimidine de novo synthesis boost the incorporation of 5FU into RNA and the formation of active nucleotides. There is currently no clinical example, but up to the end of the 1980s, Brequinar, an inhibitor of dihydroorotatdehydrogenase, was tested for this purpose.
- Synergism if Paclitaxel is given before Cisplatin [3], but after an Anthracycline, see below.

Concerning the last point, Vanhoefer et al. [3] evaluated the *in vitro* cytotoxicity of Paclitaxel and Cisplatin alone, in combination, and in sequence against established human gastric and ovarian carcinoma cell lines using 2-hour drug exposure. The combination of Cisplatin and Paclitaxel was found to be additive or even synergistic when Paclitaxel was given 24 hours prior to Cisplatin, as demonstrated by isobologram analysis. However, when both drugs were given simultaneously, or when Cisplatin was given prior to Paclitaxel, a strong antagonistic interaction was observed which was evident for up to 72 hours after a 2-hour exposure to Cisplatin. Pre-treatment with Cisplatin caused no alteration in $^{[3H]}$Paclitaxel uptake in HM2 gastric carcinoma cells, but resulted in decreased intracellular retention of Paclitaxel [3]. This phenomenon cannot be explained by pharmacokinetics, and applies in general to the combination of taxanes with platinoids, and is relevant to the adjuvant breast cancer scheme TAC–Docetaxel (T), Doxorubicine (A), Cyclophosphamide (C). The sequence of administration should be 'ACT'. In the combination of a taxane with an anthracycline, the anthracycline should be given prior to the taxane, because the converse sequence causes increased plasma levels of anthracycline and its metabolites by an unknown mechanism–leading to decreased clearance. The sequence of anthracycline prior to a taxane is even recommended in the SmPCs, for example, the use of Doxorubicine to avoid enhanced toxicities such as neutropenia and stomatitis. It is important that during the FLAG- and analogue schemes, see below (Ida-FLAG, Mito-FLAG), Ara-C has to be infused exactly four hours after the end of Fludarabine. The FLAG chemotherapy regimen consists of Fludarabine, Ara-C and granulocyte colony-stimulating factor (G-CSF). The regimen typically involves:

Fludarabine (F-Ara)	d_{1-5}	25 (-30) mg/m²
Ara-C	d_{1-5}	(1,500-) 2,000 mg/m²
G-CSF	d_{0}	400 µg/m² or 5 µg/kg till recovery

This regimen was developed following the observation that co-administration of Fludarabine with Cytarabine results in increased intracellular retention of Cytarabine's active metabolite, cytosine arabinoside-5'-triphosphate, producing a synergistic antitumour effect [4]. In addition, by increasing

cell cycling, haematopoietic growth factors are thought to improve the treatment response by rendering dormant leukaemic cells more sensitive to cytotoxic drugs [5-9]. Also, G-CSF potentiates the effects of Cytarabine by increasing its incorporation into DNA [5, 7, 8].

The same purpose – modulation of intracellular Ara-C kinetics- is behind the CLAEG-scheme, used for relapsed AML in patients over 60 years [10].

Cladribine	d $_{1-5}$	0.2 mg/kg	
Etoposid	d $_{1-5}$	60 mg/kg	from hour 2 after Cl
Ara-C	d $_{1-5}$	1.5 g/m²	from hour 6 after Cl
G-CSF	d $_{6}$	300 μg absol.	till recovery

It is named CLAEG not CLEAG

Antagonistic interactions and reduced effectiveness of methotrexate result from:

- pre-treatment with 5FU prior to MTX
- pre-treatment with Asparaginase, which blocks the effects of MTX
- pre- or simultaneous treatment with folates, which neutralise the effects of MTX [1, 2].

The order of application of cytotoxic combination schemes is important for the above-mentioned examples. For other combinations there is little robust evidence that order is significant, but arbitrarily modifying the chronology, for a more feasible daily routine for instance, is not recommended if detrimental interactions cannot be excluded unequivocally.

Infusion times

The time at which a special infusion is given depends on several factors, including the ease of venous access, whether this is central or peripheral, and the size of the infusion volume. For example, one litre of infusion fluid cannot be given in just 20 minutes through a peripheral vein. Other factors are the local tolerance of drugs. A peripheral infusion of Oxaliplatin in less than two hours, for example, will be associated with very strong pain, caused by thrombophlebitis. Infusion times over two hours are tolerated. Because of the high content of ethanol, Carmustin has to be infused over 1–2 hours. A more rapid infusion could cause flush or even bleeding of the conjunctiva.

In general, drugs in water and organic solvents are better tolerated with slower infusion rates. This is also the case with proteinaceous drugs such as monoclonal antibodies. Sometimes, a short infusion time with high peak levels are more efficient than a prolonged infusion, as in the case with Bendamustine. Owen et al. showed that high concentrations of Bendamustine are more efficient than prolonged exposure, and that a single exposure to Bendamustine was sufficient to initiate apoptosis in cancer cells, with the proportion of dead cells increasing over 72 hours (tested in cell culture) [11]. For a sufficient inhibition of thymidylate synthetase a protracted infusion time (24 hours or more) of 5FU (+ folates) is needed, as we know from Ardalan [12] and analogue schedules.

Intervals

The most effective chemotherapy intervals also depend on several factors:

- The substance and its toxicity profile–indirectly its pharmacokinetic
- The protocol–whether mono- or poly chemotherapy
- The dose and/or dose intensity–usually [mg/m²/week]

For example, 80 mg/m² of Paclitaxel can be given on a weekly basis, whereas 175 mg/m² has to be given with a three-week interval. The above-mentioned TAC scheme consists of three myelosuppressive components, with a three-week interval and often with G-CSF support.

Summary

The chronology of chemotherapeutic drugs in combination chemotherapy protocols can be very important and has to be adhered to in the above-depicted examples. The infusion time depends on drug and patient characteristics–local tolerance, venous access, and also on the pharmacokinetics and the therapeutic concept. Along with that, the toxicity profile defines the interval.

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Oral antineoplastic drugs and the role of the pharmacist

With the increasing availability and use of oral antineoplastic drugs, pharmacists are now taking a primary role in patient education and ensuring compliance with medications.

In the 1940s, cancer treatments were limited to just surgery and radiotherapy (using X-rays). It was not until the 1950s that antineoplastic drugs were discovered and approved by FDA.

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Since then, cancer survival rates have increased. Although certain cancers remain difficult to treat and are often rapidly fatal, treatment for many other types of cancer has led to longer survival and complete remission for many patients. Some cancer types such as prostate, bladder and breast cancers have become more like chronic diseases.

The goal of cancer treatment should be cure. But this is often impossible. More realistically, the main goal is usually to extend the period of disease-free survival or overall survival and improve quality of life. Oral antineoplastic drugs play an important role in improving quality of life.

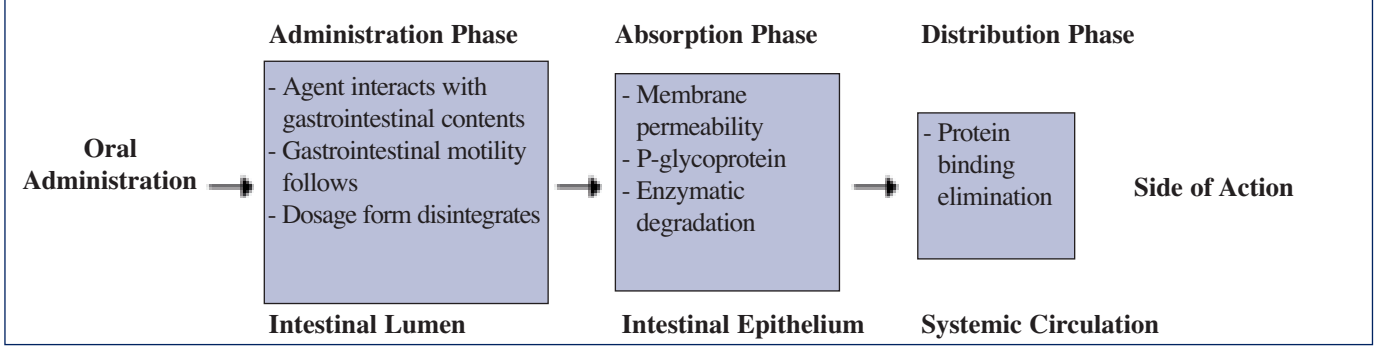
When prescribing anticancer drugs, physicians need to take into account not only the potential effectiveness of oral products, but also the preferences of patients [1, 2]. In the past, oral antineoplastic treatment was chosen over IV administration for palliative treatments; nowadays, however, oral drugs are also available as first line treatments. Patients largely prefer oral to IV treatment for the convenience of easier application and use outside the clinic [1]. But, on the other hand, patients are less likely to opt for oral treatments if there is a risk that they will be less effective, with a lower response rate, i.e. effective in fewer patients, or shorter disease-free period.

Studies to compare oral versus IV antineoplastic treatments have provided encouraging results. For example, treatment of colorectal cancer with oral fluoropyrimidine (capecitabine) showed no difference ($p < 0.05$) in overall survival, efficacy or side effects when compared to the Mayo Clinic IV regimen— the Mayo Clinic regimen is the comparator arm required by FDA for new drugs against colorectal cancer [3]. A second study compared both the effectiveness and costs of the recently available oral version of vinorelbine with IV vinorelbine, and with older drugs gemsitabine, paclitaxel, and docetaxel for the treatment of non-small cell lung cancer: oral vinorelbine treatment had the lowest cost. Furthermore, there are only slight differences in median time to progression, medial duration of survival and haematologic and non-haematologic toxicity between oral vinorelbine and older cytotoxic agents—IV vinorelbine, gemsitabine, paclitaxel and docetaxel [4].

On the whole, the little differences between oral form and IV form antineoplastic drugs in terms of cost, side effects profile, and efficacy, have been insufficient to affect treatment decisions. However, IV antineoplastics have traditionally been used more, particularly because oral forms of antineoplastic drugs have until recently had limited availability. This is due partly to the challenge of creating a formulation with suitable pharmacokinetics: IV drugs enter into the blood stream directly and circulate rapidly around the body. In contrast, oral forms are much more complicated in terms of gastric ph stability, the reproducibility of their dissolution profile, their hydrophilic/lipophilic balance, p-glycoprotein activity and enzymatic degradation, see Figure 1.

In the 1960s, there were only nine or 10 oral antineoplastics available, such as mercaptopurine, methotrexate, chlorambucil, cyclophosphamide, melphalan, hydyroxyurea, and procarbazine. At that time, angiogenesis was poorly understood and the

Figure 1: Drug absorption–from ingestion to excretion



theory of 'tumour feeding' rested on the process of vasodilation. Today, however, angiogenesis is better understood. Briefly, if there is insufficient supply of oxygen and nutrients to support a growing tumour, tumoural cells release signals which trigger new growth of blood vessels around the tumour. Research on angiogenesis has led to the discovery of new therapies aimed at blocking the actions of the molecules involved. These include antibodies and small-molecule inhibitors. The latter are available in oral forms and can enter directly into cells. One target, for example, is the intracellular enzyme tyrosine kinase which plays a key role in carcinogenesis and tumour growth. Targeted cancer therapies may be more effective than current treatments and less harmful to normal cells.

A whole plethora of targeted therapy agents has since been developed, and 30 to 35 antineoplastics are now available with targeted actions, including imatinib, dasatinib, erlotinib, sunitinib, and sorefenib.

Role of the pharmacist

After cancer diagnosis, the pharmacist's role begins. The pharmacist has to provide administration and supply the patient with the correct type and dosage of antineoplastic drug. Oral antineoplastics have many advantages but they also have some disadvantages, including the potential adverse effects of nausea and vomiting, diarrhoea, hypersensitivity, febrile neutropenia, and hand–foot syndrome [5]. Patients will have most to gain if these side effects can be managed well by the oncology team.

Oncology pharmacy checklist for managing antineoplastic drug prescriptions

Check for:

- contraindications for prescribed treatment plan
- potential drug interactions
- correct prescription for the reimbursement.

Manage:

- duration of, and time interval between, each treatment cycle
- body surface area and drug dose calculations
- information on drug handling, storage, disposal, and return of unwanted medicine
- drug safety and effectiveness
- toxicity monitoring
- patient education.

Inform patients about [6]:

- how to take the tablets – dose, time, frequency, duration of course
- possible treatment side effects and suggestions for remedial action
- what to do in case of missed doses
- importance of not sharing medicines with others
- safe storage of medicine
- obtaining repeat prescriptions and return of unused tablets to the hospital pharmacy
- wearing gloves when handling oral anticancer therapy, and minimal handling techniques
- danger of crushing tablets or opening capsules due to risk of powder inhalation
- washing hands after administering tablets.

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Oncologists urged to embrace biosimilars to help control spiralling costs of cancer care

Oncologists have been urged to embrace biosimilar drug substitution to help control the spiralling costs of cancer care. However, they have been warned that the optimal realisation of such a programme requires successful educational initiatives and the development of effective working partnerships with pharmacists and patients [1].

A literature review by researchers at Bristol University, UK, found that in many countries, cancer medicine was the leading driver of increased healthcare costs, and that taking the US as an example, direct medical spending for cancer had risen 222% in the last 20 years, faster than any other branch of medicine in developed countries over the same period [1].

These spiralling costs are unsustainable. Successful, but high-cost, cancer biologicals are helping cancer patients to survive longer, and this, coupled with an ageing and growing population, means that the cost of cancer care is rising exponentially.

For example, researchers have compared the cost over time of treating metastatic colon cancer using standard chemotherapy regimens [3]. Using the Mayo Clinic regimen of 5FU and leucovorin as a benchmark (US$63 drug cost for an eight-week treatment regimen), costs rose with each improvement. Second-generation regimens containing irinotecan or oxaliplatin cost US$9,497 to US$11,899 for an eight-week course, while third-generation regimens containing bevacizumab or cetuximab cost US$21,339 to US$30,790. The rise from US$63 to US$30,790 represented an almost 500-fold rise in drug cost (US$30,790/63 = US$488.7) [1, 2].

Given that oncologists have a WHO-stipulated duty to be part of a healthcare system that 'obtains the greatest possible level of health from the resources devoted to it, i.e. to be as cost-effective as it can be'; rationing highly effective biologicals on the basis of cost alone is not a sufficiently ethical strategy [1, 3].

This has prompted renewed calls for biological drug equivalent substitution programmes. With the help of local pharmacists, individual physicians or hospitals can save on costs of established treatment programmes with a policy of biological drug equivalent substitutions using available biosimilars [1]. Annual savings of Euros 1.6 billion per year are predicted if the EU could realise just a 20% price reduction of five patent-expired biopharmaceuticals [4].

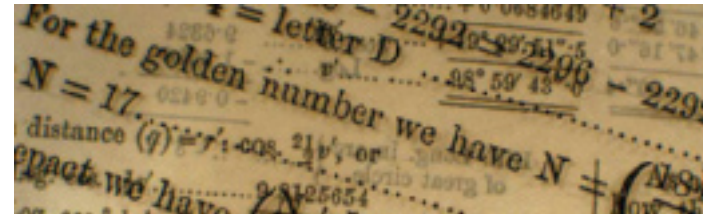
Looking forward further to 2020, there are 20 biological drugs in the EU, which will have come off patent. Biosimilar substitution could generate more than US$300 million in revenue in Europe alone. Such savings will be hard to resist, and for many countries, delaying the implementation of such programmes risks a real crisis in healthcare delivery [1].

http://www.gabionline.net/Biosimilars/Research/Oncologists-urged-to-embrace-biosimilars-to-help-control-spiraling-costs-of-cancer-car

EMA risk management plans may increase prescriber confidence in biosimilars

In the absence of observational (phase IV) data, EMA's stipulation that all marketing applications for new generation biosimilars contain individual risk management plans may help to increase prescriber confidence in the compounds [1].

The objective of a risk management plan is to protect patients from harmful events by ensuring that the benefits of a medicine exceed its risks by the greatest achievable margin. Typically, a plan consists of two parts: in part I, the safety profile of the medication is described and pharmacovigilance activities are proposed, e.g. collecting spontaneously reported adverse events, the development of post-authorisation safety studies. Part II evaluates the necessity for risk minimisation activities and provides an action plan for each potential safety concern. The proposed risk management plans for all new biosimilars are freely available on the EMA website.



Although biosimilars are 'copies' of existing biopharmaceuticals, the recombinant processes used in their manufacturing often differ from that of the originator compound. This means that despite the achievement of an identical pharmacological effect, biosimilars have the potential to cause adverse events that may not match the originator compound.

This hypothesis was proved in 1998 when a reformulated version of the innovative erythropoietin alpha product (Eprex) was launched worldwide. With such widespread use, it soon emerged that the incidence of drug- related pure red cell aplasia had increased. Although the debate surrounding the aetiology of this immunological reaction is yet to be resolved, an unfortunate lesson was learned: manipulating a biopharmaceutical formulation may put patients at risk.

Since the introduction of the EMA's risk management plans in 2005, safety-related biosimilar issues have been minimal. These successes have provided a safe foundation for confident biosimilar prescribing, with some experts believing that biosimilars can now be viewed as equally as efficacious and safe as their reference (originator) compound.

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