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Review

Lifestyle habits as a contributor to anti-cancer treatment failure

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ABSTRACT

Lifestyle may have serious consequences for cancer treatment outcome, which is a fact that both physicians and patients are often not explicitly aware of, thereby unwillingly exposing the patient to possible danger. In certain cases, patient behaviour can lead to potentially life-threatening adverse events, whilst in other cases the clinical benefit of anti-cancer therapy can be diminished. In this review, we focus on the role of certain habits (like cigarette smoking, alcohol use and the use of complementary and alternative medicine) and discuss the effects they may have on anti-cancer medication. Also patient compliance to prescribed anti-cancer drugs is a factor frequently overlooked if treatment does not follow the expectations, which gains importance with the increasingly frequent prescription of oral anti-cancer agents.

1. Introduction

To achieve a maximum therapeutic effect, cytotoxic anti-cancer drugs are typically dosed as high as possible. Therefore, based on formal phase I-studies, they are given at or close to the maximum-tolerated dose, which may lead to serious side-effects if the circulating drug exceeds certain 'toxic' threshold concentrations, a level which may vary between patients. Factors interfering with the pharmacokinetic and pharmacodynamic profile of these cytotoxic compounds may greatly increase the likelihood of the development of toxicities. In the presence of patient or disease-related risk factors (i.e. lower performance, impaired liver or kidney function, certain co-medication and older age), treating physicians have to make important choices. If drug treatment is considered, it has to be decided what type of drug should be given, and what dose can be safely administered. Given the narrow therapeutic window of most classic anti-cancer agents, factors leading to a reduced systemic exposure to these drugs should also be considered. This, in turn, may result in reduced chances of therapeutic benefit, making the choice for an optimal drug and dose even more difficult.

Most anti-cancer drugs are substrates for the hepatic cytochrome P450 (CYP) system, a group of the so-called phase I enzymes catalysing the conversion of a drug into usually inactive and non-toxic metabolites. Especially the isozymes CYP3A4 and CYP2D6 are known to play an important role in the metabolic pathways of many anti-cancer drugs. The

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function of these enzymes is extremely sensitive to biochemical alteration caused by co-medication, complementary and alternative medicines (CAM), and certain food supplements, and can result in either induced or inhibited activity (Table 1).[1,2] Several anti-HIV and anti-fungal agents, for instance, are known to strongly inhibit CYP3A4 function. If concomitantly administrated with a CYP3A4-substrate, this may lead to clinically significantly higher drug levels of the cytotoxic drug. The consequence of this process may be potentially lethal concentrations of the chemotherapeutic agent. Examples of this type of interaction are the combination of ketoconazole given concurrently with the CYP3A4 substrates

Table 1 – Selection of cytochrome P450 isozymes 2D6 and 3A4 inhibitors and inducers

CYP2D6		CYP3A4	
Inducers	Inhibitors	Inducers	Inhibitors
Dexamethasone	Bupropion[a]	Efavirenz	Indinavir[a]
Rifampicin	Fluoxetine[a]	Nevirapine	Ritonavir[a]
	Paroxetine[a]	Phenytoin	Clarithromycin[a]
	Quinidine[a]	Rifampicin	Itraconazole[a]
		St. John's wort	Ketoconazole[a]
			Aprepitant[b]
			Fluconazole[b]
			Erythromycin[b]
			Grape fruit juice[b]

a Known as strong inhibitors (capable to cause a >5-fold increase in plasma area under the curve or >80% decrease in clearance).
b Known as moderate inhibitors (capable to cause a >2-fold increase in plasma area under the curve values or 50–80% decrease in clearance).
c Data based on the cytochrome P450 drug-interaction table, available at: http://medicine.iupui.edu/flockhart/table.htm (version 4.0, released 8/20/2007).

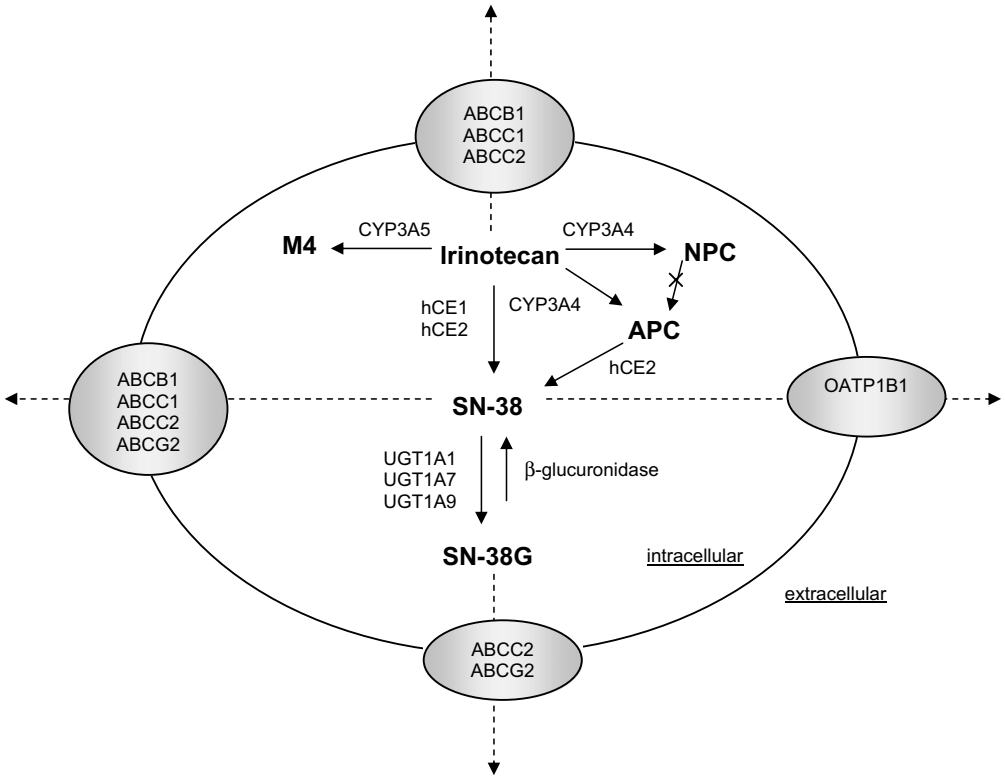

Fig. 1 – Irinotecan elimination pathways. *Abbreviations*: ABCB1, P-glycoprotein (MDR1); ABCC1, multidrug resistance protein 1 (MRP1); ABCC2, canalicular multispecific organic anion transporter (c-MOAT; MRP2); ABCG2, breast cancer resistance protein (BCRP); APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin; CYP3A4, cytochrome P-450 isoenzyme 3A4; hCE1/2, carboxylesterase isoforms 1 and 2; M4, metabolite 4; NPC, 7-ethyl-10-(4-amino-1-piperidino)-carbonyloxycamptothecin; OATP1B1, organic anion-transporting polypeptide isoform 1B1; SN-38, 7-ethyl-10-hydroxycamptothecin; SN-38G, 10-O-glucuronyl-SN-38; UGT1A1/7/9, uridine diphosphate-glucuronosyltransferase 1A1, 1A7, and 1A9 isoforms.

irinotecan and docetaxel.[3,4] In contrast, such agents as the bactericide rifampicin can induce CYP3A activity. When given combined with anti-cancer drugs primarily metabolised by CYP3A, such as gefitinib and imatinib,[5] increased metabolism can occur, potentially resulting in drastically reduced concentrations of the active compound commensurate with therapeutic failure.

In addition to CYPs, the class of phase II enzymes can also be involved in anti-cancer drug metabolism, typically through conjugation reactions. The interaction of anti-cancer drugs with such enzymes can lead to increased complexity of elimination pathways. For example, the elimination of irinotecan is regulated in part by both CYP3A4 and UDP-glucuronosyltransferase 1A (UGT1A)-mediated metabolism (Fig. 1). Both pathways are associated with extensive interindividual variability due to the concurrent use of co-medication influencing the function of one or both enzyme systems.[6]

Lastly, a group of proteins facilitating drug transport (phase III proteins), including efflux-drug pumps (i.e. ATP binding cassette (ABC)-transporters such as P-glycoprotein

Table 2 – Effect of commonly used CAM on the activity of enzymes and transporters in humans

Herb	Effect
Asian ginseng (*Panax ginseng*)	Weak inhibition of CYP2D6, CYP3A4; no influence on CYP1A2, CYP2E1
Balloon vine (*Cardiospermum halicacabum*)	Potential inhibition of CYP1A2
Bitter orange (*Citrus aurantium*)	No influence on CYP1A2, CYP2D6, CYP2E1, or CYP3A4
Black cohosh (*Actaea racemosa*)	Weak inhibition of CYP2D6; no influence on CYP1A2, CYP2E1, CYP3A4, ABCB1
Black pepper (*Piper nigrum*)	Potential inhibition of CYP3A4, ABCB1
Bloodwort (*Sanguisorba officinalis*)	Potential induction of CYP1A2
Boldo-funigreek (*Peumus boldus*)	Potential inhibition of CYP2C9
Chinese skullcap (*Scutellaria baicalensis*)	Potential inhibition of CYP3A4, ABCB1
Cranberry (*Vaccinium macrocarpon*)	No influence on CYP2C9, CYP3A4, ABCB1
Dandelion (*Taraxacum mongolicum*)	Potential induction of CYP1A2
Danshen (*Salvia miltiorrhiza*)	Potential inhibition of CYP2C9; potential induction of CYP3A4
Devil's claw (*Harpagophytum procumbens*)	No conclusive data available
Dogbane (*Apocynum venetum*)	No influence on CYP3A4, ABCB1
Dong quai (*Angelica sinensis*)	Potential inhibition of CYP2C9
Echinacea (*Echinacea* spp.)	Potential induction of CYP3A4; no influence on CYP1A2, CYP2D6, CYP2E1
Fennel (*Foeniculum vulgare*)	Potential induction of CYP1A2
Feverfew (*Tanacetum parthenium*)	No conclusive data available
Fo-ti (*Polygonum multiflorum*)	No conclusive data available
Garlic (*Allium sativum*)	Weak inhibition of CYP3A4, CYP2E1, ABCB1; weak induction of N-acetyl-transferase
Gan cao (*Glycyrrhiza uralensis*)	Potential induction of CYP2C9, CYP3A4
Ginger (*Zingiber officinalis*)	No influence on CYP2C9
Ginkgo (*Ginkgo biloba*)	Strong induction of CYP2C19; weak inhibition of CYP3A4; no influence on CYP2C9
Goldernseal (*Hydrastis Canadensis*)	Strong inhibition of CYP2D6 and CYP3A4
Grapefruit juice (*Citrus paradise*)	Strong inhibition of (intestinal) CYP3A4
Grape seed (*Vitis vinifera*)	Potential induction of (hepatic) CYP3A4
Green tea (*Camellia sinensis*)	No influence on CYP2D6, CYP3A4; potential induction of CYP1A2
Guar gum (*Cyamopsis tetragonoloba*)	No influence on ABCB1
Guggul tree (*Commiphora mukul*)	Potential induction of CYP3A4
Horny goat weed (*Epimedium* spp.)	No conclusive data available
Japanese arrowroot (*Pueraria lobata*)	Potential inhibition of ABCC and OAT transporters
Kangen-Karyu	Potential inhibition of CYP2C9
Kava kava (*Piper methysticum*)	Strong inhibition of CYP2E1; strong induction of CYP3A4
Licorice (*Glycyrrhiza uralensis*)	Potential inhibition of CYP3A4
Milk thistle (*Silybum marianum*)	No influence on CYP1A2, CYP2D6, CYP2E1, CYP3A4, ABCB1
Peppermint oil (*Mentha piperita*)	Weak inhibition of CYP3A4
Pomelo juice (*Citrus grandis*)	Weak inhibition of CYP3A4 or ABCB1 (or both)
Red clover (*Trifolium pratense*)	No conclusive data available
Saw palmetto (*Serenoa repens*)	No influence on CYP1A2, CYP2D6, CYP2E1, CYP3A4
Shoseiryuto (schisandra/ephedra/cinnamon)	No influence on CYP3A4
Siberian ginseng (*Panax quinquefolius*)	No influence on CYP2D6, CYP3A4
Soy (*Glycine max*)	No influence on CYP3A4
St. John's wort (*Hypericum perforatum*)	Strong induction of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4, ABCB1
Tanner's Cassia (*Cassia auriculata*)	Potential inhibition of CYP1A2
Tortoise shell (*Quilinggao*)	Potential induction of CYP2C9
Turmeric (*Curcuma longa*)	No influence on CYP3A4, ABCB1
Valerian (*Valeriana officinalis*)	No influence CYP1A2, CYP2D6, CYP2E1, CYP3A4
Wheat bran (*Triticum aestivum*)	No influence on ABCB1; potential inhibition of CYP3A4
White peony (*Radix paeoniae alba*)	No influence on CYP3A4
Wolfberry (*Lycium barbarum*)	Potential inhibition of CYP2C9
Wu-Wei-Zi (*Schisandra chinensis*)	Potential induction of CYP2C9, CYP3A4
Wu-Chu-Yu (*Evodia rutaecarpa*)	Potential induction of CYP1A2

(ABCB1), breast cancer resistance protein (BCRP; ABCG2) and c-MOAT (ABCC2)), responsible for the elimination of xenobiotics out of cells, may also be involved in drug elimination. Depending on their tissue distribution pattern, co-medication influencing the function of such transporters may result in different effects on elimination. For instance, functional inhibition of efflux transporters like ABCB1 and ABCG2 in the intestine may result in increased systemic concentrations of an orally administered drug, whereas at the same time inhibition at the tumour level may lead to increased cytotoxicity. Induction of the expression of ABC transporters is also relatively common and is known to occur after administration of carbamazepine.[7] This process may result in reduced intestinal absorption and/or increased clearance and cause sub-optimal circulating concentrations of anti-cancer drugs. Furthermore, the function of uptake transporters, such as organic anion-transporting polypeptides (OATPs), may be influenced by co-medication, making the pharmacokinetic profile of many anti-cancer drugs essentially unpredictable a priori in case of multiple co-treatments. In addition to its CYP3A inducing capability, rifampicin is also known as an inhibitor of the uptake transporter OATP1B1,[8] which may therefore result in confusing outcomes, as described for the combination with atrasentan.[8,9]

In view of the above considerations, it should come as no surprise that drug interactions are an important source of in-

Table 3 – Suspected interaction of St. John's wort with anti-cancer drugs

Anti-cancer drug	Main proteins involved in drug absorption and/or elimination	Expected effect of chronic St. John's wort co-administration
6-Mercaptopurine	Thiopurine methyltransferase, ABCC4	None
6-Thioguanine	N/a	None
Anastrazole	CYP2C9, CYP3A4	Decreased exposure
Arsenic trioxide	Non-CYP methylation	None
Asparaginase	N/a	None
Bleomycin	N/a	None
Busulfan	CYP3A4	Decreased exposure
Capecitabine	Carboxylesterases, cytidine deaminase	None
Carboplatin	N/a	None
Chlorambucil	ABCC2	Decreased exposure
Cisplatin	ABCC2	Decreased exposure
Cyclophosphamide	CYB2B6, CYP2C9, CYP3A4	Decreased exposure
Cytarabine	Cytidine deaminase	None
Dacarbazine	CYP2E1	Decreased exposure
Docetaxel	CYP3A4, CYP3A5, ABCB1	Decreased exposure
Doxorubicin	CYP3A4, CYP2D6, ABCB1	Decreased exposure
Epirubicin	CYP3A4	Decreased exposure
Erlotinib	CYP3A4, CYP1A2, ABCB1, ABCG2	Decreased exposure
Estramustine	N/a	None
Etoposide	CYP3A4, ABCB1, ABCC1, ABCC2	Decreased exposure
Exemestane	CYP3A4	Decreased exposure
Fluorouracil	Dihydropyrimidine dehydrogenase	None
Gefitinib	CYP3A4, ABCG2	Decreased exposure
Gemcitabine	Deaminases	None
Hydroxyurea	N/a	None
Ifosfamide	CYP2B6, CYP3A4	Decreased exposure
Imatinib	CYP2C9, CYP2C19, CYP3A4, ABCB1, ABCG2	Decreased exposure
Irinotecan	CYP3A4, CES2, UGT1A1, ABCC2, ABCG2	Decreased exposure
Ixabipelone	CYP3A4	Decreased exposure
Letrozole	CYP2A6, CYP3A4	Decreased exposure
Melphalan	N/a	None
Methotrexate	ABCC1, ABCC2, ABCG2	Decreased exposure
Mitomycin C	N/a	None
Mitoxantrone	ABCB1, ABCG2	Decreased exposure
Oxaliplatin	N/a	None
Paclitaxel	CYP3A4, CYP2C8, ABCB1	Decreased exposure
Tamoxifen	CYP2B6, CYP3A4, CYP1A2, CYP2E1	Decreased exposure
Temozolomide	N/a	None
Teniposide	CYP3A4, ABCB1	Decreased exposure
Thiotepa	N/a	None
Topotecan	CYP3A4, ABCB1, ABCG2	Decreased exposure
Tretinoin	CYP2C8, CYP2C9, CYP3A4	Decreased exposure
Vinblastine	CYP2D6, ABCB1	Decreased exposure
Vincristine	CYP3A4, CYP3A5, ABCB1	Decreased exposure
Vinorelbine	CYP3A4	Decreased exposure

Abbreviation: N/a, information not available.

tra- and interindividual pharmacokinetic variability. It has been estimated that such interactions account for up to 10% of hospitalisations and a substantial proportion of treatment-related deaths.[10,11] Given the high risk of potentially severe complications of such interactions, extreme caution is warranted with the use of concurrently administered drugs or alternative medicine, either prescribed or self-administered, during systemic anti-cancer treatment to optimise therapeutic efficacy whilst minimising the incidence and severity of unwanted side-effects.

2. Complementary and alternative medicine

In recent years it has become evident that, next to concurrently prescribed medicine, also compounds not officially classified as a drug may significantly influence anti-cancer drug elimination, and therefore lead to unwanted interactions. The best studied compounds in this category belong to the class of complementary and alternative medicines (CAM), which are considered as a group of medicinal and health care systems, practices and products not part of conventional medicine.[12] CAM can be divided into several categories, including biologically based therapies (i.e. herbs, vitamins and diet). As a result of not being considered a drug, CAM are easily available to patients over the counter through drugstores, health shops and delivered by online suppliers.[2]

Cancer patients are common users of CAM, for divergent reasons.[2] Income, sex, educational level, socio-economic status, religion, ethnicity, age, type of cancer and earlier CAM use all influence the willingness of patients to resort to CAM.[2,13,14] Especially young and higher educated women are inclined to resort to these therapies. In addition, CAM use is positively related with the use of chemotherapy and a higher stage of disease. Estimates of 25–84% (biologically based) CAM use, some time after the malignancy is diagnosed, have been made for cancer patients in the United States.[2,14] Mostly patients choose to combine, rather than replace, conventional and experimental anti-cancer treatment with CAM.

Unfortunately, patients often do not realise that these products may interfere with regular treatment, like cytotoxic chemotherapy. As CAM is believed by many to contain natural products, a possibly negative or harmful interaction is often not considered. In spite of the long history of CAM usage by oncology patients, many metabolic interactions between prescription drugs and CAM have come to light only relatively recently. Despite this fact, and although the drug interaction potential of CAM has not yet been assessed exhaustively, knowledge is now expanding rapidly (Table 2). Amongst the most widely used biologically based CAM, St. John's wort (SJW; *Hypericum perforatum*), an herb with anti-depressant activity, is of special interest. This product contains the substance hyperforin, which is known to cause a strong induction of CYP3A4 activity (Table 1).[15,16] In one study involving cancer patients, it was shown that SJW caused a 42% decrease in the plasma concentration of the active irinotecan metabolite SN-38.[17] Combinations of SJW with imatinib (in healthy volunteers) and docetaxel (*in vitro*) have similarly shown significantly altered pharmacokinetic profiles of the anti-cancer drugs.[18,19]

Since SJW can modulate the function of many other enzymes and drug transporters, SJW interactions are not limited to these examples, but may be relevant in many other cases too (Table 3).

Although not supported by clinical data, a number of other CAM can be expected to influence anti-cancer drug elimination based on their ability to interfere with elimination pathways *in vitro*.[20] Therefore, patients should be advised to be extremely cautious in combining CAM with anti-cancer treatment until safety is proven for specific combinations (Table 4).

Table 4 – Specific CAM to discourage and avoid during chemotherapy

Herb	Concurrent chemotherapy/condition (suspected effect)
Echinacea	Caution with camptothecins, cyclophosphamide, TK inhibitors, epipodophyllotoxins, taxanes, and *Vinca* alkaloids (CYP3A4 induction)
Ephedra	Avoid with all cardiovascular chemotherapy (synergistic increase in blood pressure)
Ginkgo	Caution with camptothecins, cyclophosphamide, TK inhibitors, epipodophyllotoxins, taxanes and *Vinca* alkaloids (CYP3A4 and CYP2C19 inhibition); discourage with alkylating agents, anti-tumour antibiotics and platinum analogues (free-radical scavenging)
Ginseng	Discourage in patients with oestrogen-receptor positive breast cancer and endometrial cancer (stimulation of tumour growth)
Green tea	Discourage with erlotinib (CYP1A2 induction)
Japanese arrowroot	Avoid with methotrexate (ABCC and OAT inhibition)
Soy	Avoid with tamoxifen (antagonism of tumour growth inhibition), and treatment of patients with oestrogen-receptor positive breast cancer and endometrial cancer (stimulation of tumour growth)
St. John's wort	Avoid with all concurrent chemotherapy (CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4 and ABCB1 induction)
Valerian	Caution with tamoxifen (CYP2C9 inhibition), cyclophosphamide and teniposide (CYP2C19 inhibition)
Kava-kava	Avoid in all patients with pre-existing liver disease, with evidence of hepatic injury (herb-induced hepatotoxicity) and/or in combination with hepatotoxic chemotherapy; caution with camptothecins, cyclophosphamide, TK inhibitors, epipodophyllotoxins, taxanes and *Vinca* alkaloids (CYP3A4 induction)
Grape seed	Caution with camptothecins, cyclophosphamide, TK inhibitors, epipodophyllotoxins, taxanes and *Vinca* alkaloids (CYP3A4 induction), and with alkylating agents, anti-tumour antibiotics and platinum analogues (free-radical scavenging)

Abbreviation: TK, tyrosine-kinase.

3. Cigarette smoking

Smoking behaviour has been linked to induction of more than 10 different types of cancer, and it is responsible for 9 out of 10 lung cancer deaths.[21,22] Although the relationship between smoking and cancer genesis is no longer a question of debate, the pharmacokinetic effects of smoking on cancer therapy have only been scarcely explored so far. This may be due to the fact that relatively little attention has been paid to smoking behaviour during anti-cancer treatment, whilst data estimate that during and following cancer treatment 25–30% of patients are current smokers.[23,24]

Data obtained from a heterogeneous group of more than 25,000 cancer patients, have suggested a difference in 5 year survival rates, favouring non-smokers over smokers (44% versus 55%, respectively).[25] In line with this finding, other data show that female patients who continue to smoke after a diagnosis of non-small cell lung cancer have a higher mortality rate.[26] Likewise, patients suffering from head and neck cancer who continue smoking may have a shorter period of survival, and have a higher chance of disease recurrence or a second malignancy, compared to patients who quit smoking.[27,28] A variety of explanations to these findings may be given; a pharmacokinetic effect on anti-cancer treatment may be part of these explanations. This is a plausible explanation because cigarette smoke contains numerous constituents known to interact with drug metabolising enzymes and transporters (Fig. 2).[29–33]

Recently, for two important anti-cancer drugs (erlotinib and irinotecan), the effect of cigarette smoking on their metabolism was studied. The clearance of erlotinib was shown to be 24% higher in smokers compared to non-smokers,[34] which may negatively affect overall survival in (non-small cell) lung cancer patients treated with this epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.[35] This difference in clearance was attributed to an interaction at the CYP1A level. Cigarette smoke constituents are also capable to induce some isoforms of the UDP-glucuronosyl transferase family.[31] This enzyme system is responsible for the conjugation of bilirubin, and might explain the lower levels of unconjugated bilirubin in smokers compared to non-smokers.[36–38] As mentioned before, the active irinotecan metabolite SN-38 is subject to UGT1A-mediated metabolic conversion. In 190 patients with advanced cancer treated with irinotecan, it was shown that the concentrations of SN-38 were 40% lower in smokers relative to non-smokers.[39] In addition, a striking reduction (from 38% to 6%) of treatment-induced grade 3 and grade 4 neutropaenia was seen in smokers. Further investigation is required to assess the influence of smoking behaviour on the anti-tumour activity of chemotherapeutic drugs.

4. Alcohol use

Irrespective of gender, a limited use of alcohol has been shown to be related to lower overall mortality.[40] Nonetheless, an increased relative risk for developing cancer is demonstrated for heavy drinkers, although this relationship is clearly confounded by smoking behaviour.[41] Particularly, head and neck cancer and oesophageal carcinoma have been related to this lifestyle.[42,43] In line with smoking, for tumours which are related to alcohol use, the chance of disease recurrence or a second malignancy is higher in patients who persevere drinking after being diagnosed or treated. A study showed that also alcohol-using breast cancer patients appear to have a higher mortality rate compared to those completely abstaining from alcoholic beverages.[44]

Prolonged alcohol consumption is known to induce CYP2E1 activity,[45] whilst a single dose of ethanol may down-regulate CYP2E1 mRNA in mice.[46] Since this CYP plays only a minor role in the metabolism of anti-cancer drugs, pharmacokinetic effects of concomitant use of 'alcohol' alone due to CYP2E1-mediated alterations are expected to be limited. More importantly, evidence is emerging that alcohol may modulate CYP3A activity. For example, it has been shown that moderate alcohol consumption does not change the systemic clearance but reduces the oral bioavailability of midazolam by

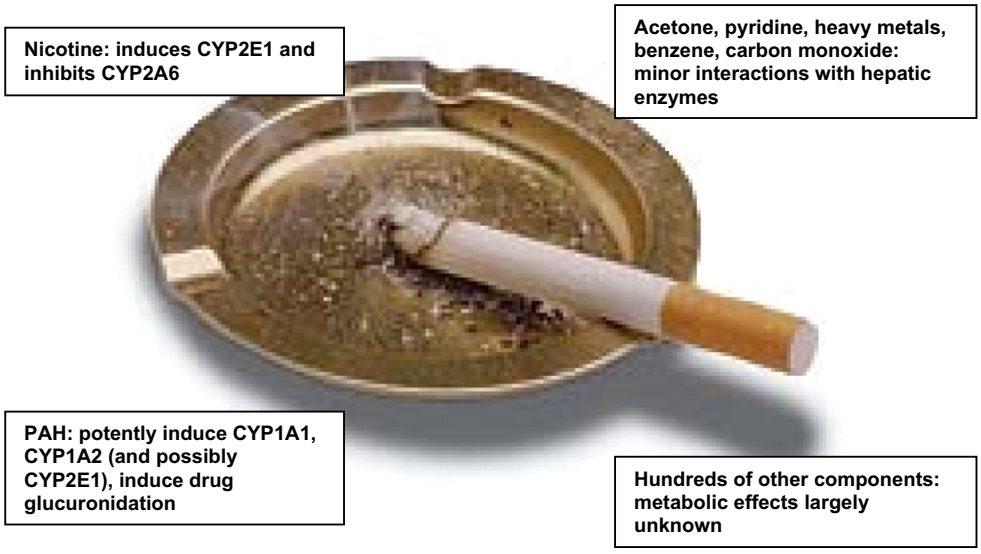

Fig. 2 – Assumed metabolic effects resulting from cigarette smoke components. *Abbreviations*: CYP: cytochrome P450, PAH: polycyclic aromatic hydrocarbons.

26%, consistent with intestinal CYP3A induction.[47] Using a CYP3A activity test, it was demonstrated that the level of CYP3A activity was higher in individuals using alcohol.[48] The theory of CYP3A induction was recently consolidated by experiments in mice.[49]

Apart from alcohol, drinks may contain other substances influencing drug metabolism. For example, red wine contains flavonoids and other polyphenolic ingredients, potentially responsible for drug interactions. Some flavonoids have been shown to inhibit ABC transporter-mediated cellular efflux,[50,51] whereas other flavonoids may have opposite effects.[52] Uptake transports like OATP1B1 and OATP1A2 may also be modulated by flavonoids.[53,54] Some years ago, it was demonstrated that concomitant intake of red wine caused a 50% increase in the clearance of cyclosporine, attributed to a decreased absorption.[55] Given the potential interactions on the level of both drug metabolising enzymes and drug transporters, and the current lack of good clinical (interaction-) studies, it should be discouraged to use alcohol before and during anti-cancer treatment. In contrast to some other recommendations, including those associated with CAM usage and smoking, this advice is usually widely accepted by the public, requiring less persuasiveness.

5. Medication compliance

In all types of anti-cancer therapy, whether chemotherapy, endocrine therapy or immunological therapy is involved, oral agents have gained an important place in standard treatment regimens. A further shift from intravenous to oral therapy for cancer is expected. Oral treatment clearly has advantages over intravenous therapy, such as improved quality of life, and a decreased hospitalisation.[56] It is also largely preferred by patients over other routes of drug administration.[56] However, it also has less favourable consequences. Optimal dosing-schedules have been derived during trials, but have not been corrected for sub-optimal patient adherence to these drugs, as patients joining the initial trials may be more adherent than current users. Adherence (or compliance) to oral anti-cancer drugs is variable and difficult to predict, as rates vary widely (from less than 20% to 100%).[57,58] The seriousness of the disease does not guarantee adherence as shown for breast-cancer patients advised to use tamoxifen,[59] although compliance is generally higher in cancer patients compared to other diseases.[60] Adherence measured by patient self-reports and pill-counts likely overestimates true adherence as shown by a study using a microelectronic monitoring device.[59] In a study by Partridge et al. including nearly 2400 patients, 23% missed taking tamoxifen on >20% of the days studied during the first year of treatment.[61] During the next years, adherence rates dropped to 50% in the fourth year of therapy. In another study, elderly women with early stage breast cancer using hormonal therapy were followed, in which 17% of them discontinued tamoxifen treatment during a two-year follow-up period.[62] Even in case adherence is considered to be relatively adequate (87% adherence to an analgesic compound), as studied in cancer patients with nociceptive pain caused by a malignancy, a considerable variation in the time of intake of the drug was noticed.[63]

Table 5 – Factors affecting cancer patient adherence

Reasons for non-adherence	Example
Patient-related reasons	Expectations towards therapy Knowledge of the disease Perception of the disease Attitude Age Ethnicity Social-economic class Religion
Disease-related reasons	Type of malignancy Symptoms Curative/palliative setting Earlier failure of therapy Co-morbidity
Therapy-related reasons	Duration of therapy Perception of risks Perception of benefit Side-effects Amount of pills (a day/per gift) User-friendly
Others	Support from a pharmacy/family doctor Frequent visit to an oncologist Interaction between patient and physician Education

Age, race, history of mastectomy and a recent visit to an oncologist all influence adherence rates.[61] Perception of risks and benefits of tamoxifen therapy seems critical for sustaining adherence to this drug. Other factors, which may affect adherence to drug therapy, include the patient's knowledge of the disease, his/her beliefs and attitudes about health, the interaction between patient and health care providers, and the patient's social and financial resources (Table 5).[64–66] Only once this problem is better recognised, can interventions be implemented to prevent and deal with poor adherence. Educational programmes, behavioural modification programmes, pill boxes and medication diaries might help improving adherence, although we have to be sceptic towards its efficacy. Already numerous attempts have been made to improve adherence during the last decades, showing that comprehensive interventions are more effective than single focused interventions.[67,68] Physicians should at least never blindly assume adherence, as every patient might be at risk for non-adherence. Therefore, patients should be actively asked for (non-)adherence, problems with pill taking and their expectations towards therapy.[57] For long-term regimens, it remains important to rediscuss adherence, even if the patient seems to be adherent, as these patients might become non-adherent ones.[68]

6. Conclusions

Patients will usually not undergo an anti-cancer treatment before a thorough physical and laboratory check has been done, as poor performance and impaired liver or kidney function are known to seriously affect therapy, potentially leading to severe side-effects. This is because physicians are keen to minimise all possible circumstances leading to extra co-morbidity and mortality to the best of their abilities. It is therefore sour to

notice that patients are capable to nullify the exact considerations made by their physician to prevent an inadequate and toxic therapy. And clearly it is usually not the patient's intention to interact with the metabolism of the anti-cancer drug in question, but pure ignorance about the possible dangers of lifestyle effects leads to this behaviour.

In some cases, it is impossible to prevent a metabolic interaction, for instance if the patient has to use co-medication for which no alternative is available. In that case, in good consultation with a physician, adequate and rational dose-adjustments can be made. In the case of CAM use and smoking, it is much more difficult to discuss its use and its potential unwanted negative effects with the patient, as these topics might be emotionally charged. In addition, having an illegal status, the use of cannabis was a subject not easily discussed for a long time. Since its use is allowed for medicinal purposes in several countries now, we have become aware of the real extent of its usage.[69,70] The use of other soft-drugs remains consequently foggy, even if explicitly asked for. And clearly in the case of adherence, patients will also not easily admit to have been deviated from the original instructions for drug use.

Even food compounds, for example, grapefruit juice, star fruit, broccoli, Brussels sprouts, caffeine and char-grilled meat, are capable to influence anti-cancer drug metabolism based on several mechanisms.[71,72] We realise that it is impossible to cope with all these factors in daily practice. But at least, the take home message of this review paper should be an 'awareness' of the possible effects of lifestyle habits on anti-cancer drug therapy by both patients and health care physicians.

Conflict of interest statement

None declared.

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