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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).

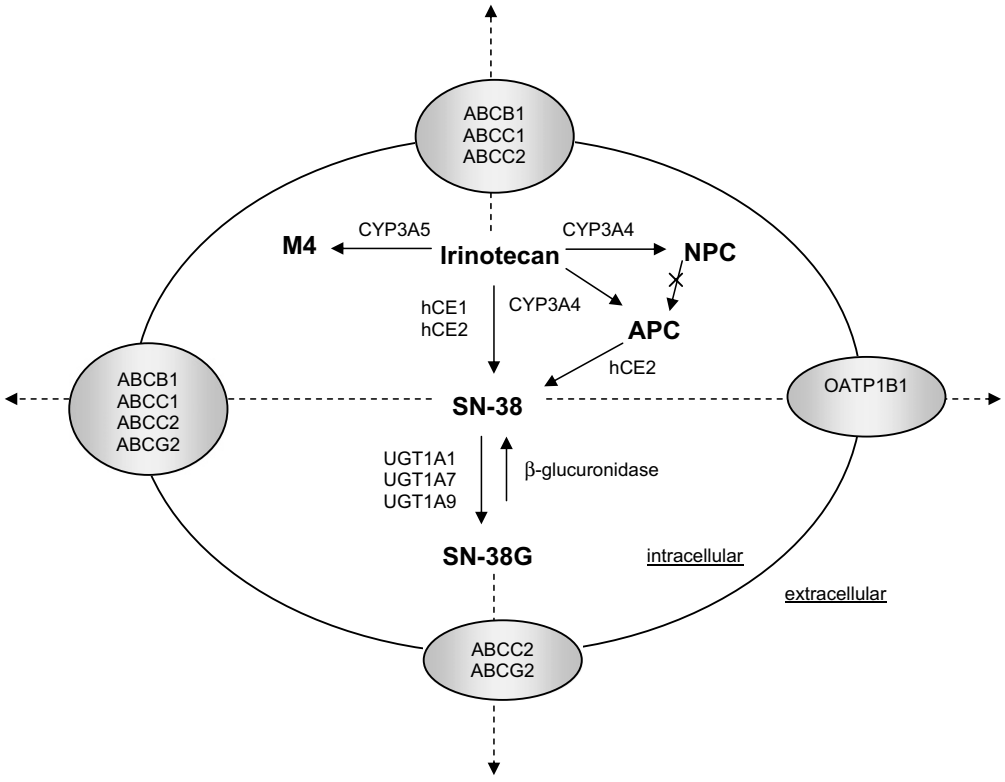

Fig. 1 – Irinotecan elimination pathways. *Abbreviations*: ABCB1, P-glycoprotein (MDR1); ABCC1, multidrug resistance protein 1 (MRP1); ABCC2, canalicular multispecific organic anion transporter (c-MOAT; MRP2); ABCG2, breast cancer resistance protein (BCRP); APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin; 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.