COURSE: GENETIC FACTORS IN EFFECTIVE DRUG USE

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TOPIC: Pharmacogenetic Applications in Cancer and Psychiatric Drugs

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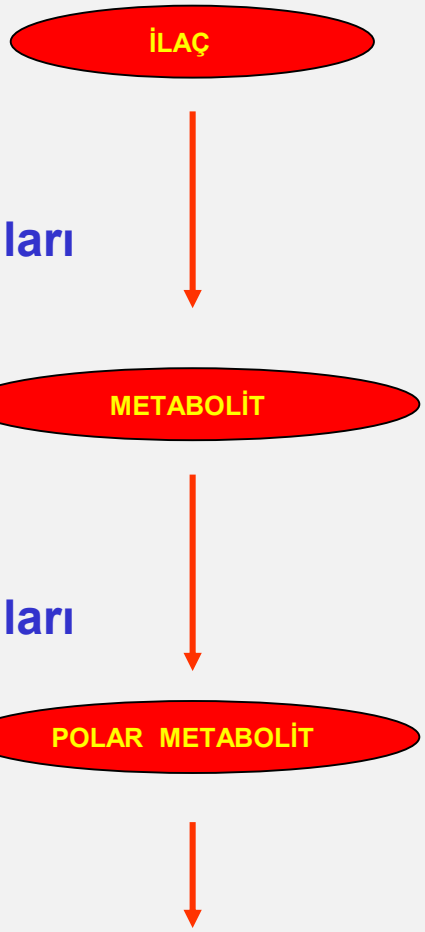


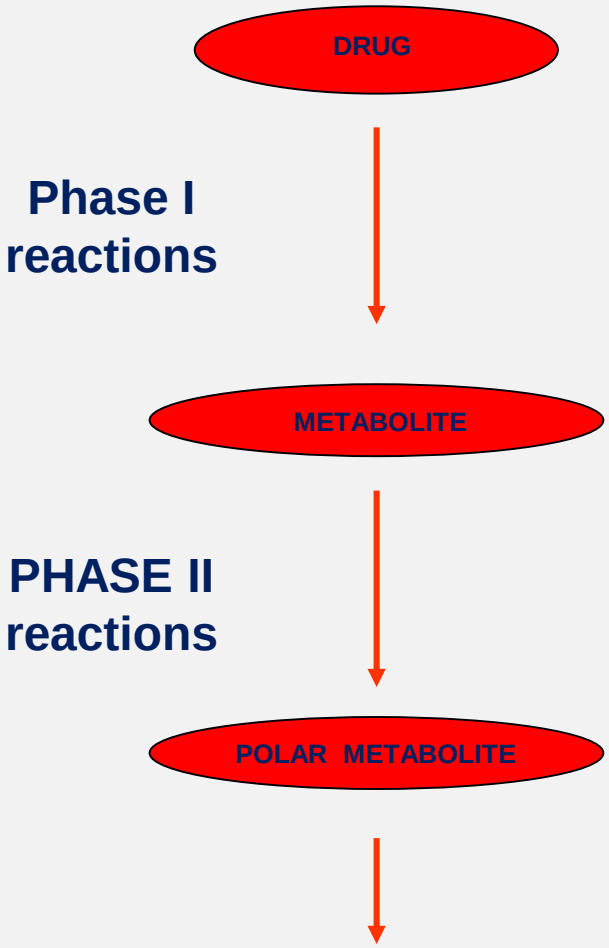
FAZ I: oksidasyon, redüksiyon, hidroliz

Faz I enzimleri:
Sitokrom P450
Alkol dehidrogenaz
Monoamin oksidaz
Epoksit hidrolaz

FAZ II: konjügasyon

Faz II enzimleri:
Glutatiyon S-transferaz
UDP glukuronozil transferaz
N-asetil transferaz
Sulfotransferaz

İlaçların genel biyotransformasyon şeması



PHASE I: oxidation, reduction, hydrolysis

Phase I enzymes:
Cytochrome P450s,
Alcohol dehydrogenase,
Monoamine oxidase,
Epoxy hydrolase,

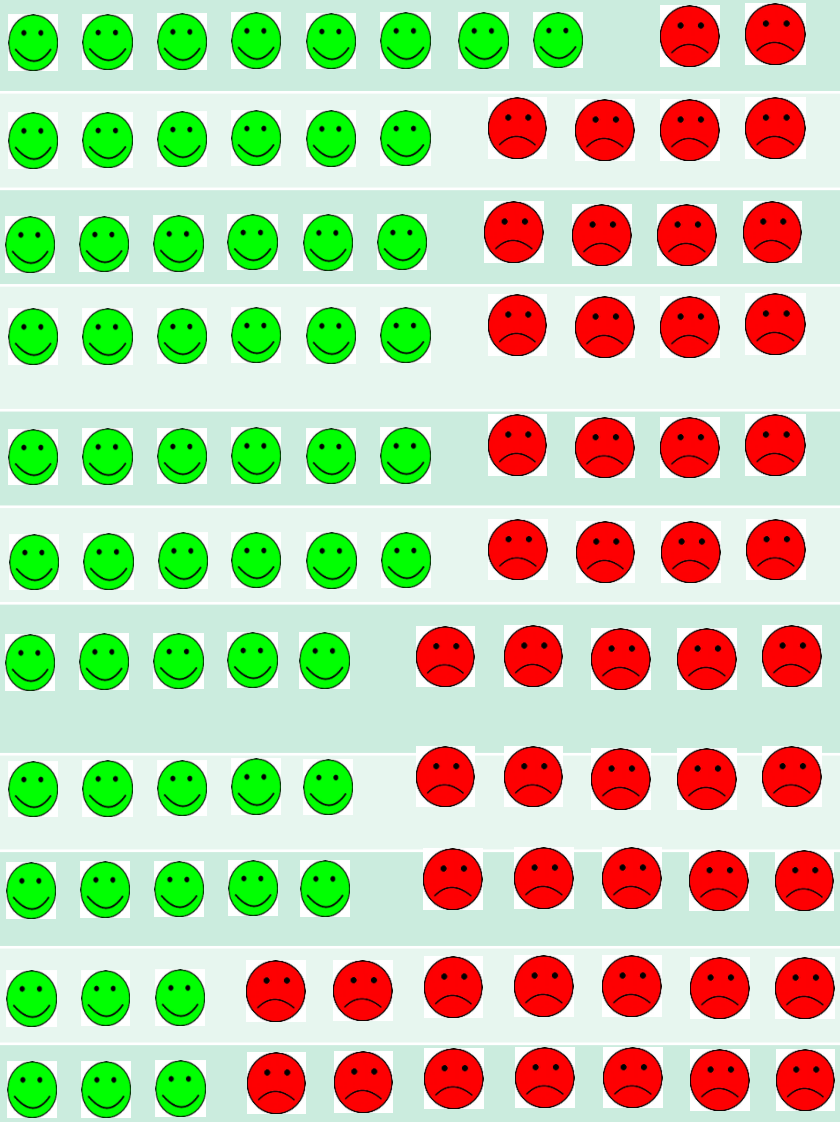
PHASE II: conjugation

Phase II enzymes:
Glutathione S-transferase
UDP glucuronosyl transferase
N-acetyl transferase
sulfotransferase

General biotransformation of drugs

Interindividual differences in drug RESPONSE

THERAPEUTIC AREA	EFFICACY RATE (%)
Analgesics (COX-2)	80
Depresssion (SSRI)	62
Asthma	60
Cardiac Arrythmias	60
Schizophrenia	60
Diabetes	57
Migraine (prophylaxis)	50
Rheumatoid arthritis	50
Osteoporosis	48
Alzheimer	30
Oncology	25



Why pharmacogenetic applications are critical in cancer treatment:

1. Anticancer drugs generally have a narrow therapeutic range,
2. Some antineoplastics are prodrugs and enzymes that turn them into active compounds have genetic polymorphisms,
3. Active metabolites are generally associated with toxicity,
4. Some anticancer drugs are detoxifed with polymorphic enzyme system,
5. Most of the drugs in cancer treatment among patients show pharmacokinetics and toxicity differences.

I. DRUG METABOLIZING ENZYMES

II. POLYMORPHISMS IN DRUG CARRIER ENZYMES

III. PROTEINS RELATED TO DRUG TARGETS

IV. DNA REPAIR ENZYMES

Absorption
Distribution
Metabolism
Excretion

Drug targets
Disease related pathways

Pharmacokinetics + **Pharmacodynamics** → **Drug response / Toxicity**

Drug metabolising enzymes
Drug transporters

Enzymes
Receptors
Ion channels
Lipoproteins
Coagulation factors

DNA → RNA → Protein → Activity (Function: increase or decrease)

I. DRUG METABOLIZING ENZYMES

Genetic polymorphisms in Phase I enzymes

CYP2A6	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP3A4 / 5
Tegafur	Cyclophosphamide	Paclitaxel	Cyclophosphamide	Teniposide	Cyclophosphamide
	Ifosfamide	Tegafur	Ifosfamide	Thalidomide	Ifosfamide
	Tamoxifen		Tamoxifen		Docataxel
					Doxorubicin
					Etoposide
					Paclitaxel
					Teniposide
					Vincristine
					Vinblastaine

I. DRUG METABOLIZING ENZYMES

Genetic polymorphisms in Phase II enzymes

1. **Glutathion S-transferases (GSTs):**

A. **GSTM1,**

B. **GSTT1,**

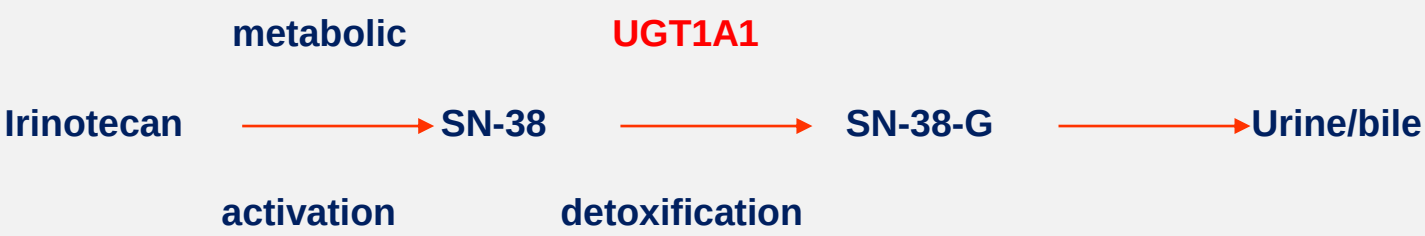
C. **GSTP1.**

I. DRUG METABOLIZING ENZYMES

Genetic polymorphisms in Phase II enzymes

Uridine diphosphate glucuronosyl transferase (UGT): **It acts in the excretion of many lipophilic xenobiotics and endobiotics by glucuronidation.**

Pharmaceuticals: Irinotecan (Campto), Epirubicin (Epirubicin Ebewe, Farmorubicin), Etoposide (Etoposide, Lastet, Vepesid)

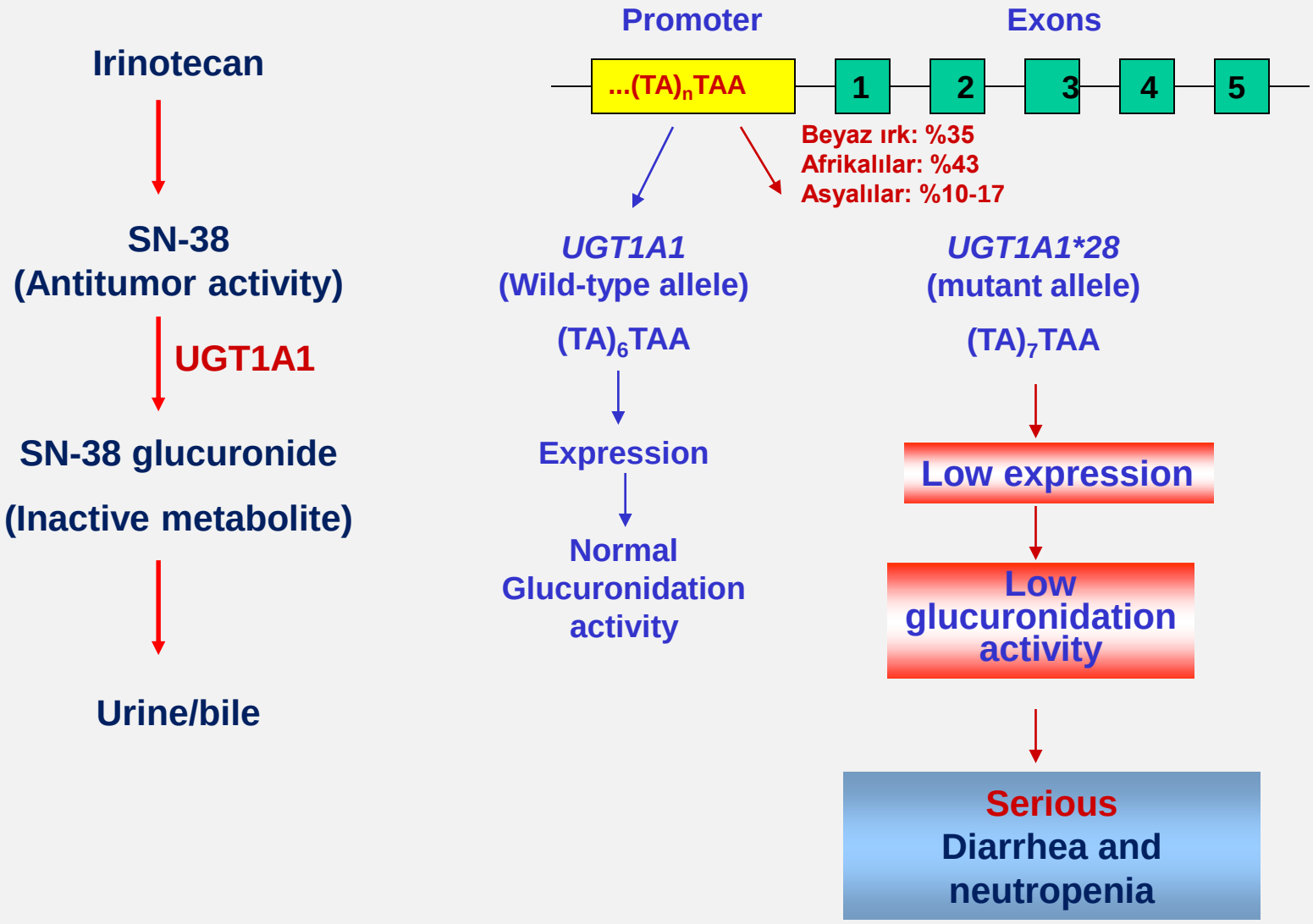


Chromosome: 2

Allele : *UGT1A1*28* (promoter region TA repeats)

***In vivo* / *in vitro*: Low expression ve enzyme activity**

Note: Diarrhea and neutropenia occur in 20-35% of patients treated with irinotecan..


Irinotecan
SN-38
(Antitumor activity)
UGT1A1
SN-38 glucuronide
(Inactive metabolite)
Urine/bile
Promoter
Exons
...(TA)nTAA
1
2
3
4
5
Beyaz ırk: %35
Afrikalılar: %43
Asyalılar: %10-17
UGT1A1
(Wild-type allele)
(TA)6TAA
Expression
Normal
Glucuronidation
activity
UGT1A1*28
(mutant allele)
(TA)7TAA
Low expression
Low
glucuronidation
activity
Serious
Diarrhea and
neutropenia

II. POLYMORPHISMS IN DRUG CARRIER ENZYMES

1. ABCB1 (P-glycoprotein-MDR1),
2. ABCC1 (Multidrug resistance-proteins, MRP1),
3. ABCG2 (Breast cancer resistance protein-BCRP),
4. Organic anion carrier polypeptides (OATP),
5. Organic anion carriers (OAT).

Substrates: Actinomycin D, Daunorubicin, Docetaxel, Doxorubicin, Etoposide, Gefitinib, Irinotecan, Paclitaxel, Teniposide, Topotesan, Vinblastin, Vinkristin Diflomotesan (BN-80915), Epirubicin, Flavopiridol, Imatinib,

IV. DNA REPAIR ENZYMES

1. Repair of DNA lesions: dacarbazine, bis-chloroethylnitrozourea, streptozotocin, temozolomide.

2. Base excision repair: mitomycin C, mafosfamide, chlorambusil.

3. Nucleotide excision repair: cis-platinum, chlorambucil.

4. DNA mismatch repair: cis-platinum, doxorubicin, etoposide, busulfan, procarbazine, temozolomide

5. Double-strand fracture repair: nitrogen-mustard, chlorambusil

- **XRCC1 enzyme:**
- **ERCC1 and ERCC2 enzymes:**

Thiopurine S-methyltransferase (TPMT) polymorphism - 6-mercaptopurine and azathiopurine

As a result of polymorphisms in the gene encoding TPMT enzyme, very serious toxicity can develop. It is necessary to reduce the dose or not to use the drug.

DRUG	GENE	PATIENT GROUP	Section of SmPC
Capesitabin	DPYD	DPD deficiency	Contraindications, Warnings and precautions
Nilotinib	UGT1A1	UGT1A1*28	Warnings and precautions, clinical pharmacology
Cisplatin	TPMT	TPMT slow metabolisers	Clinical pharmacology, Warnings and precautions
Dabrafenib	G6PD	G6PD deficiency	Warnings and precaution, adverse drug reactions
Panitumumab	KRAS	KRAS mutation	Indication and use
Tamoxifen	F5	Factor V Leiden carriers	Warnings

DRUG	GENE	BIOMARKER	SITUATION	USAGE
Afatinib	EGFR	Efficacy	Mandatory	EGFR exon 19 deletion or exon 21 L858R mutation Positive
Arsenic trioxit	PML/RARA	Efficacy	Mandatory	PML/RARα gene expression positive
Cefuximab	EGFR	Efficacy	Mandatory	EGFR protein expression positive
Cefuximab	EGFR	Efficacy	Mandatory	KRAS codons 12 and 13 mutation negative
Dabrafenib	BRAF	Efficacy	Mandatory	BRAF V600E mutasyon positive

PSYCHIATRIC DRUGS

Psychiatric drugs with pharmacogenetic biomarker in SmPC (n = 24

İLAÇ	Genetik Bilgi
Amitriptyline	CYP2D6 PM
Aripiprazole	CYP2D6 PM
Atomoxetine	CYP2D6 PM
Citalopram	CYP2C19 PM
Clomipramine	CYP2D6 PM
Clozapine	CYP2D6 PM
Desipramine	CYP2D6 PM
Diazepam	CYP2C19 PM
Doxepin	CYP2D6 PM
Fluoxetine	CYP2D6 PM
Fluvoxamine	CYP2D6 PM
Iloperidone	CYP2D6 PM
Imipramine	CYP2D6 PM
Modafinil	CYP2D6 PM
Nefazodone	CYP2D6 PM
Nortriptyline	CYP2D6 PM
Paroxetine	CYP2D6 EM
Perphenazine	CYP2D6 PM
Pimozide	CYP2D6 PM
Protriptyline	CYP2D6 PM
Risperidone	CYP2D6 PM
Thioridazine	CYP2D6 PM
Trimipramine	CYP2D6 PM
Venlafaxine	CYP2D6 PM

Drugs containing pharmacogenetic information in the section on Posology and Administration in SmPC (n = 6)

Psychiatric drug	Gene	SmPC
Aripiprazole	CYP2D6 PM	Posology and method of administration, Pharmacological properties
Atomoxetine	CYP2D6 PM	Posology and method of administration, Warnings and precautions, Drug interactions, Pharmacological properties
Citalopram	CYP2C19 PM	Posology and method of administration, Pharmacological properties, Warnings ,
Clozapine	CYP2D6 PM	Posology and method of administration, Pharmacological properties
Iloperidone	CYP2D6 PM	Posology and method of administration, Warnings and precautions, Drug interactions, Pharmacological properties
Pimozide	CYP2D6 PM	Posology and method of administration, precautions