Praxisrelevante Interaktionen und Supportivtherapie

1. ASORS Jahreskongress 31.10.2009 Workshop VI

Dr. HP Lipp
Chefapotheker des Universitätsklinikums Tübingen

Overview

- **Substance-related Adverse effects**
  - Cytotoxic drugs *versus* Targeted Therapy
  - Spectrum and severity of side effects
  - Dose modifications & Supportive agents
- **Drug Interactions**
  - Physico-chemical –
  - Clinical-pharmacokinetic –
  - Pharmacodynamic -

Spectrum of side effects

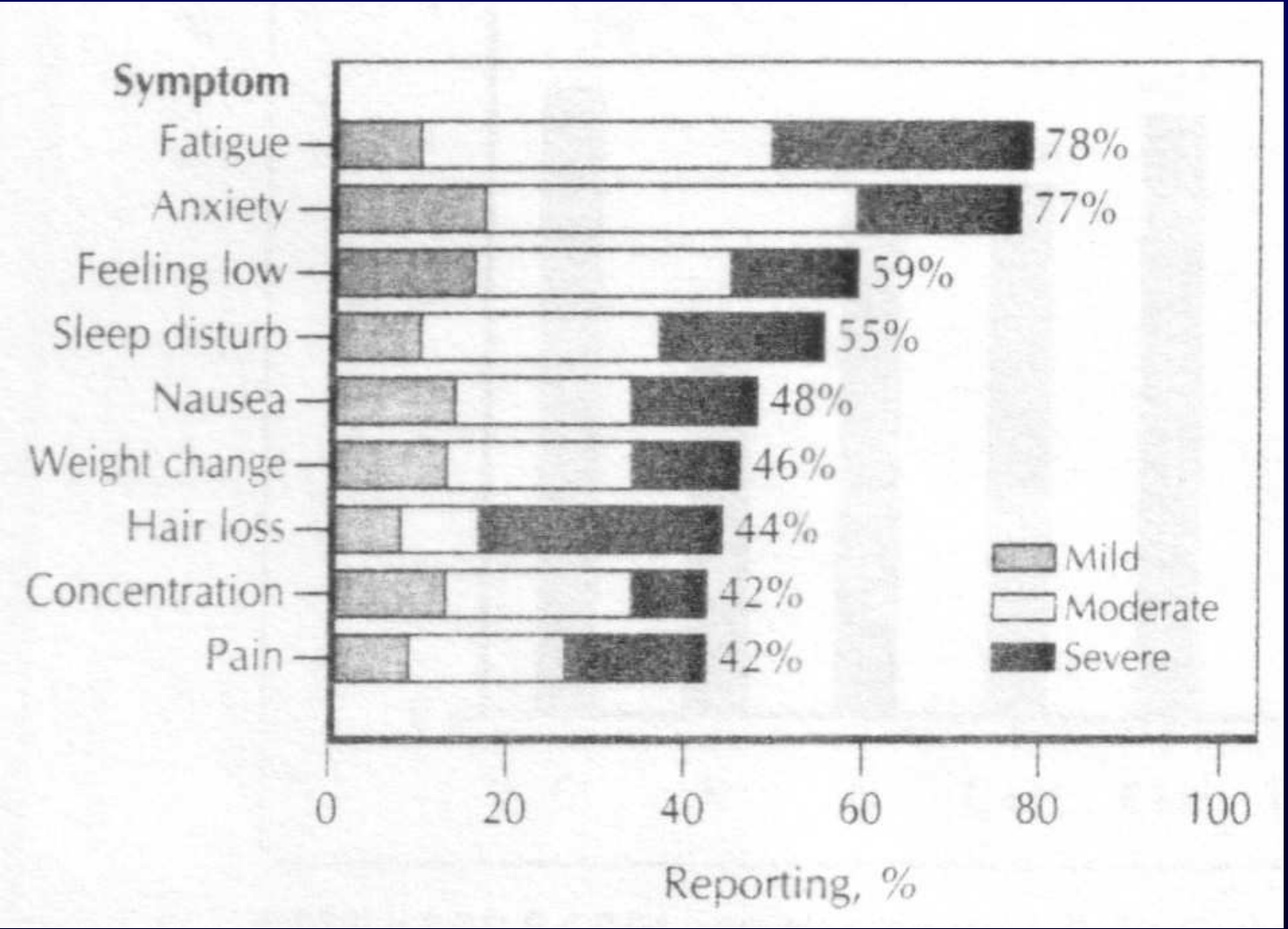
- **Cytotoxic drugs (Cancer chemotherapy)**
  - Chemically heterogenous group of agents with an impact on different constitutive cell proliferation rate between cancer cells and normal cells (limited selectivity!)
  - Conclusion: Consider dose-dependent toxicity on rapidly proliferating normal cells and substance-related effects
- **Targeted Therapy (Individualized regimen)**
  - Tumor-specific molecular defects (oncogenes and their resulting oncoproteins) rather than proliferation rate are decisive for anticancer drug efficacy
  - Conclusion: Normal cells with a constitutive role of the corresponding proto-onocogenes and proteins can be damaged in a dose-dependent manner

Toxicity of Cancer Chemotherapy – Overview

- **Toxicity of rapidly proliferating normal tissues**
  - Emesis and Nausea
  - Myelosuppression (e.g. neutropenia, thrombocytopenia)
  - Mucositis, Diarrhea,
  - Alopecia, Dermatologic Toxicity (e.g. onycholysis)
- **Ulcerationen by accidental Extra/Paravasation**
- **Hypersensitivity Reactions**
  (caused by drugs themselves or adjuvants)
- **Substance-related Organ Toxicity**
  - Nephro- and Urotoxicity (e.g. Cisplatin, Ifosfamide)
  - Neurotoxicity (e.g. Ifosfamide, Oxaliplatin, MTX)
  - Pulmonary Toxicity (e.g. Blemoycin, Busulfan)
  - Cardiotoxicity (e.g. Anthracyclines, HD Cyclophosphamide)
  - Hepatotoxicity (e.g.z.B. Asparaginase, Busulfan)
- **Late Side effects of Cancer Chemotherapy**
  -Infertility, Secondary Malignancies, Teratogenicity

Cancer patients experiences

Ashbury et al (J.Pain Symptome Manage 1998; 16; 298-306)



CTX Toxicity on Rapidly Proliferating normal cells

Supportive management - overview

Side effect	Causative agent (Example)	Supportive strategy
Nausea/ Vomiting	Cisplatin, Dacarbazine, AC, EC (Risk factors!)	5HT3 antagonist (d1) Dexamethasone (d1-4) Neurokinin-Antagonist (d1)
Neutropenia	Docetaxel, Pemetrexed	G-CSF preparations
Anemia	Cisplatin	Epoetin preparations
Thrombo-cytopenia	Carboplatin	Platelet concentrates Romiplostim?
Mucositis	Methotrexate HD-Chemotherapy	Folinic Acid Palifermin (rec. KGF)?
Onycholysis	Docetaxel	Local cooling

Pilot project: Aprepitant vs. Olanzapine

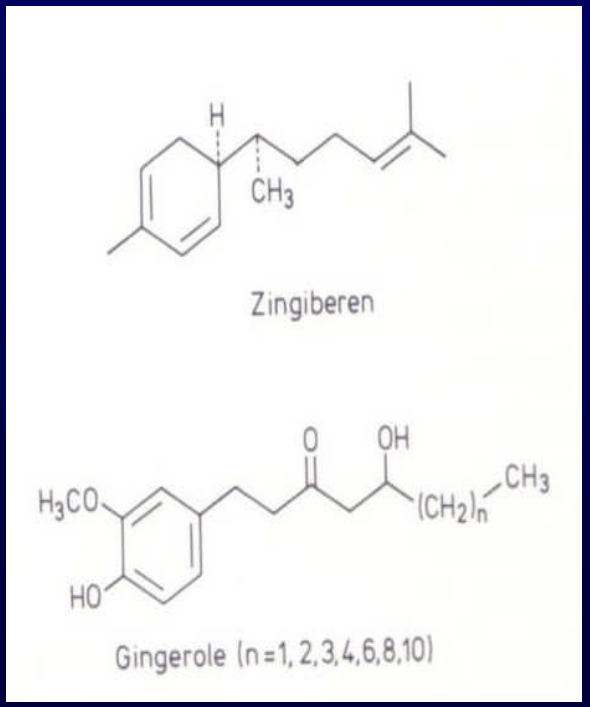
	Treatment arms					
	D-2	**D-1**	**D1**	**D2**	**D3**	**D4**
Standard arm	Placebo	Placebo	Aprepitant 125mg po Decadron 12mg IV Palonosetron .25mg IV	Aprepitant 80mg po Decadron 4mg po bid	Aprepitant 80mg po Decadron 4mg po bid	Placebo Decadron 4mg po bid
Experimental arm	Olanzapine 5mg po	Olanzapine 5mg po	Olanzapine 10mg po Decadron 12mg IV Palonosetron .25mg IV	Olanzapine 10mg po Decadron 4mg po bid	Olanzapine 10mg po Decadron 4mg po bid	Olanzapine 10mg po Decadron 4mg po bid

Treatment medications were blinded from patients and providers using black gel capsules

Conclusion: similar efficacy and safety (Shumway et al. ASCO 2009 #9633)

Ginger supplementation

Daily doses of 0,5-1 g (d-3 to d+3) significantly aids in reduction of nausea during the 1st day of CTX (#9511)



Open question:

Impact on CTX efficacy?

Anticancer Drug-Related Organ Toxicity

Supportive management - overview

Side effect	Causative agent	Supportive strategy
Urotoxicity	Cyclophosphamide Ifosfamide	Mesna
Cardiotoxicity	Anthracyclines (conventional form)	Dexrazoxan: 1:10 (FDA), 1:20 (EMEA) with Doxorubicin
Nephro-toxicity	Cisplatin	Mg-Subst.,Hydration, Osmodiuresis
Neurotoxicity	Oxaliplatin	Calcium/Magnesium, Venlafaxine (NaSRI)
HSR	Paclitaxel (Taxol)	H1-, H2-antihistaminic agent, Dexamethasone

Accidental CTX overdosages

Case reports (mod. from Lipp HP DAZ 1999; 139: 4430-7)

INN	Prescription error	Consequence
Cisplatin	480 mg IV (instead of Carboplatin)	Renal failure, ototoxicty, emesis
Lomustin (CCNU)	600-1100 mg within 4 days (instead of 130 mg/m^2 q6w)	Pancytopenia, Multiorgan dysfunction
Cyclophosph-amide	4 g/m^2/day d1-4 (instead of 1 g/m^2/day d1-4)	Heart failure
Methotrexate	10 mg p.o. daily (instead of 10 mg q7d)	Mylelosuppression severe mucositis
Vincristine	0.7-3 mg i.th. (instead of i.v.)	Encephalopathy, coma

Overdose with 6400 mg of imatinib: is it safe?

Bhargav R. et al. Ann Oncol 2007; 18: 1750-1

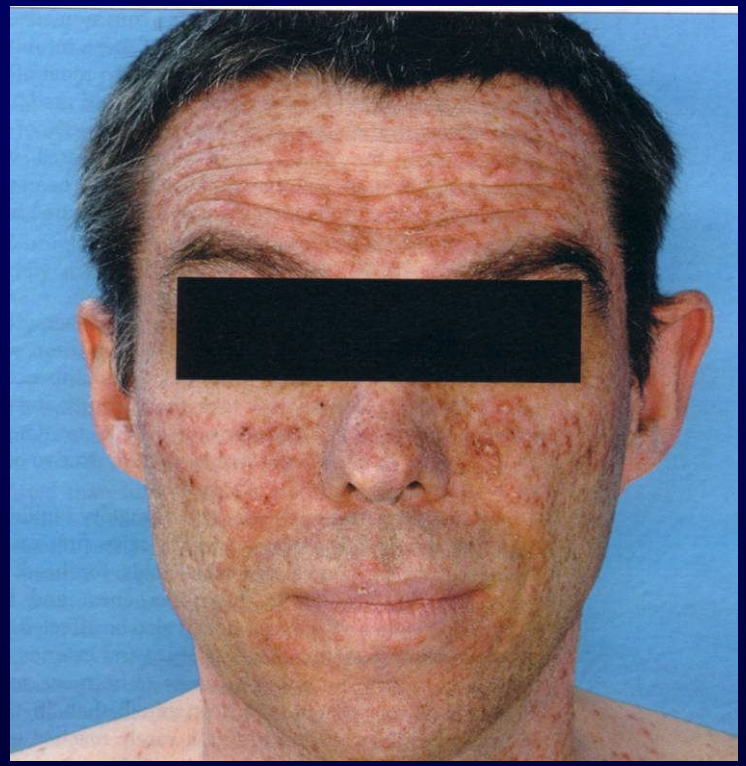
A suicidal attempt with 6400 mg of Imatinib (16 x 400 mg) by a young 21-year old female CML patient without…substantial side-effect is reported. This also highlights 6400 mg of imatinib is not lethal.

Six hours after ingestion she had severe nausea (20-25/d), abdominal pain, fever, swelling of face and lips which progressed for 2 days. After 5 days she became afebrile.

A psychiatric evaluation showed that the patient was suffering from depression and she received treatment for the same.

Targeted Therapy in Clinical Oncology

Anti EGF Therapeutics and Dermatologic Toxicity



- Akneoid reactions: A common feature during treatment with EGF-targeted drugs like

- Cetuximab (Erbitux)
- Panitumumab (Vectibix)
- Erlotinib (Tarceva)
- Gefitinib (Iressa)

Supportive agents in discussion: clindamycin 1% gel, benzoylperoxide 5% gel, minocyclin 2x200 mg p.o./Tag (do not use retinoids topically or orally); Dry skin: Eucerin c.aqua

STEPP: role of prophylactic supportive agents?

Table 4. Side-effects (grade ≥3) from panitumumab 6 mg/kg IV q2w (mod. from[8])

Side-effect	Panitumumab/BSC	BSC
Skin-related toxicities	14%	0%
Abdominal pain	7%	5%
Dyspnoea	5%	3%
Hypomagnesaemia	3%	0%

Table 5. Incidence of panitumumab-related grade ≥3 skin toxicity and the role of prophylactic versus reactive skin treatment according to the STEPP trial (mod. from[12])

	Prophylactic skin treatment	Reactive skin treatment
Patients	n = 48	n = 47
Total number of Panitumumab doses	155	141
Dermatitis acneiform	4%	21%
Pruritus	2%	11%
Pustular rash	4%	17%
Paronychia	2%*	6%

*Grade 4 toxicity

Overview

- **Substance-related Adverse effects**
  - **Cytotoxic drugs *versus* Targeted Therapy**
  - **Spectrum and severity of side effects**
  - **Dose modifications & Supportive agents**
- **Drug Interactions**
  - **Physico-chemical –**
  - **Clinical-pharmacokinetic –**
  - **Pharmacodynamic -**

Drug Interactions in Clinical Oncology

Physiko-chemical Interactions

- Possible incompatibilities when different drug-containing solutions are combined with each other, preparation of oral suspensions

Clinical-pharmacokinetic interactions

- Drug absorption – role of concomitant food intake or gastric pH values, cytochrome-P450 dependent and – independent metabolism, renal or biliary excretion

Pharmacodynamic drug interactions

- Overlapping drug toxicity during combination
- Synergistic, additive and antagonistic inetractions on the cellular level

Mod. nach Kämmerer & Mutschler INTENSIVMEDIZIN IM DIALOG 1-91

Current recommendations

- **Intake on an empty stomach (1 h a.c. or p.c.)**
  - **Busulfan, Lomustin, *Melphalan (85% vs. 58%)*, Temozolomid (Magen-pH!), Hydroxyurea, Methotrexat, 6-Mercaptopurin, Thioguanin, Tegafur/Uracil(UFT)**
  - **Sorafenib, Nilotinib, Erlotinib, *Lapatinib***
- **Intake with food**
  - **Chlorambucil (30-60 min a.c.), Treosulfan, Alltransretinsäure, Capecitabin (30 min p.c.), Idarubicin (20 min p.c.), Mitotan, Vinorelbin**
  - **Imatinib, Thalidomid (1h p.c., zur Nacht)**
- **Intakte with or without food**
  - **Cyclophosphamid, Procarbazin, Trofosfamid, Etoposid, Fludarabin, Topotecan**
  - **Dasatinib, Gefitinib, Sunitinib, Lenalidomid**

Influence of gastric pH on TKI absorption

TKI	Coadministration	Comment
Imatinib	Concomitant use of 40 mg omeprazole daily	Use of PPI does not affect imatinib AUC
Nilotinib	Concomitant use of 40 mg Esomeprazole	Nilotinib c_{max} and AUC reduced by 27% and 34% - clinical consequence?
Dasatinib	Famotidine 40 mg (A) +2h or (B) -10h before TKI	TKI exposure is reduced by -60% via (B) or antacids – avoid combination!

Beumer JH et al. ASCO 2009 #2503; Gallagher NJ et al. ASCO 2009 #7053; Eley et al. J Clin Pharmacol 2009; 49: 700-9

Cave: Fluoropyrimidines and Brivudin!

18 deaths after introduction of Sorivudine (Okuda et al. JPET 1998)

Cancer Chemotherapy: Metabolic drug interactions

Cytochrome P450 *independent* pathways

Target enzyme	Substrate	Potential Interaction
Xanthin-oxidase	6-Mercaptopurine Azathioprine	Allopurinol p.o.
DPDH	Fluoropyrimidine	Brivudine, Sorivudine (Prodrug)
UGT1A1	Irinotecan (CPT11)	Smoking (PAH)

Abbreviations:

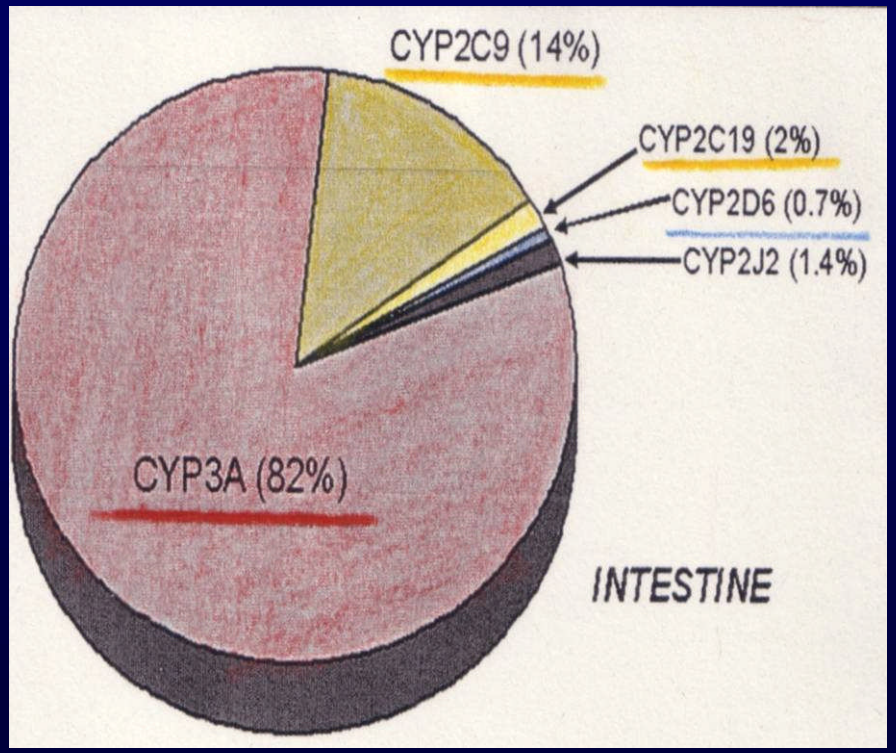
DPDH (Dihydropyrimidine Dehydrogenase, UGT1A1 (Uridinediphosphateglucuronosyltransferase Isozyme 1A1, PAH (Polycyclic aromatic hydrocarbons)

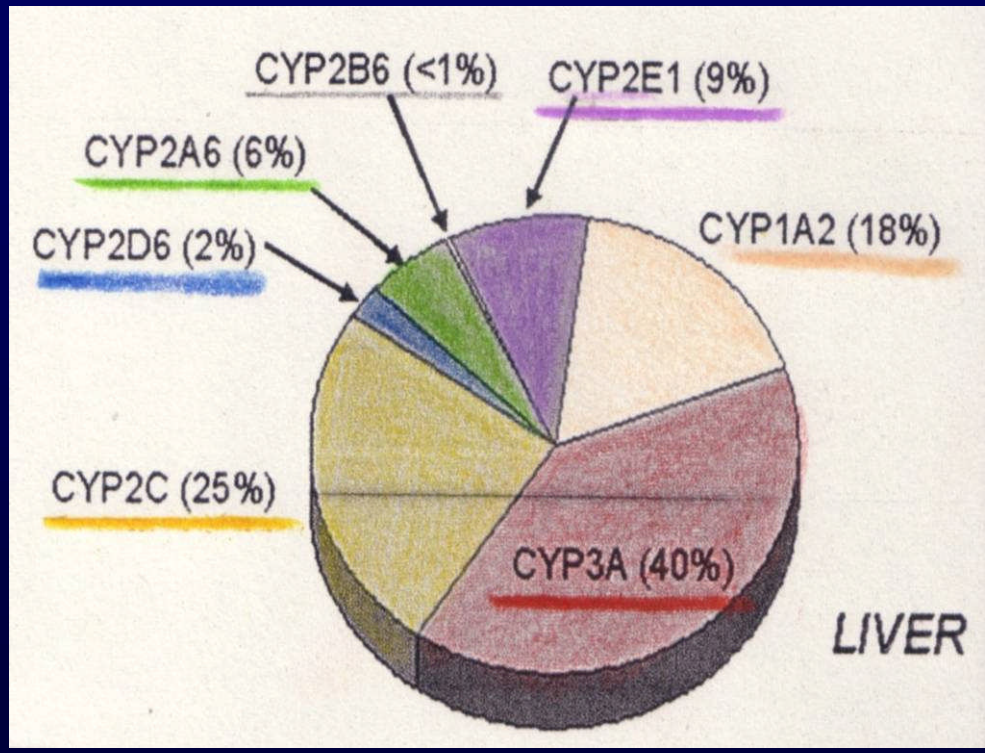
Mod.: Lipp HP, Onkologie 2007; 13: 801-812,

Cytochrome P450 Isozymes

Extra- and intrahepatic distribution

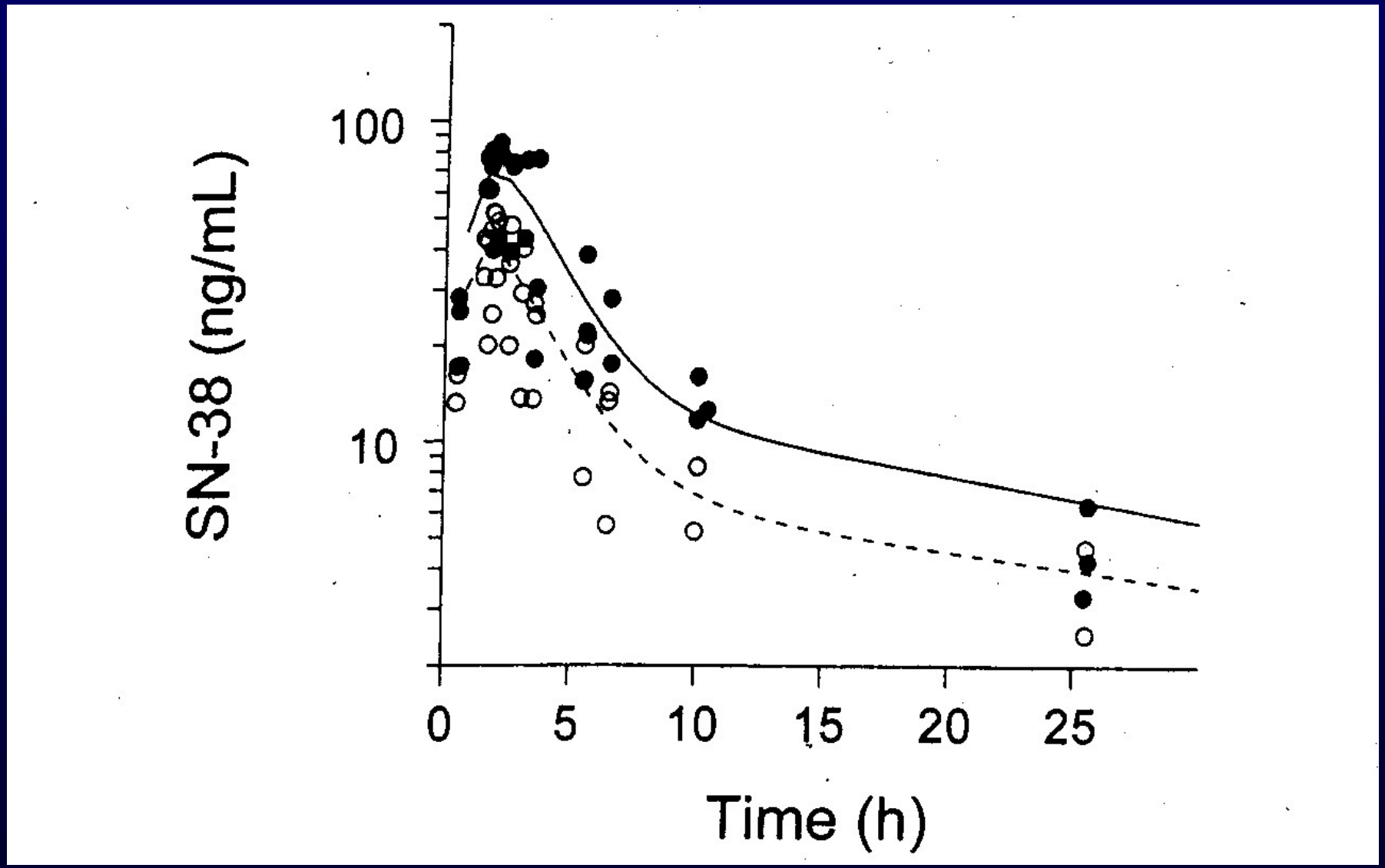
Mod. from: Drug Metabolism and Disposition 2006; 34(5)





Auswahl: Cyp1A1, Cyp1A2; Cyp2A6, Cyp2B1, Cyp2B6, Cyp2C8, Cyp2C9, Cyp2C18, Cyp2C19, Cyp2D6, Cyp2E1, Cyp3A4, Cyp3A5

John´s wort: interaction with CPT-11 metabolism



R. Mathijssen et al. JNCI 2002: 300 mg t.i.d.; start: d(-14); AUC (SN38): -42%

Enzyme-Inducing Antiepileptic Drugs (EIAED)

Impact on c_{min} of Imatinib and CGP74588 in Glioblastoma patients

Comedication	Imatinib	CGP47588
No	1404 ± 899	356 ± 186
Levetiracetam	1369 ± 640	347 ± 123
Valproic Acid	1399 ± 664	355 ± 117
Phenytoin	380 ± 266	268 ± 196
Carbamazepine	473 ± 358	240 ± 137
Oxcarbazepine	534 ± 193	216 ± 86
Topiramate	722 ± 199	291 ± 140
Lamotrigine	1466 ± 405	431 ± 107

Pursche S et al. Current Clin Pharmacol 2008; 3: 198-203

Clinical pharmacokinetics of Temsirolimus

Differential effects of ketoconazole

Pharmacokinetic parameter	Sirolimus (TEM 5 mg)	Sirolimus (TEM 5 mg + KETO 400 mg)
C_{max} (ng/ml)	13,3	29,0
t ½ (h)	74.8	112.8
AUC (hxng/ml)	1204	3889

Conclusion: Strong Cyp3A4 inhibitors should be avoided during Temsirolimus 25 mg IV q7d. If one is necessary, a dose reduction to 12.5 mg weekly should be considered. If the strong inhibitor is discontinued, a washout period of ca. 1 week should be allowed, before Temsirolimus 25 mg is restarted (JP Boni et al. Br J Cancer 2008).

Ondansetron & Cyclophosphamide

Does Ondansetron have a significant impact on CP Kinetics?

- **Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics**
  - Cagnoni PJ et al. BMT 1999; 24: 1-4
- **Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer**
  - Gilbert CJ et al. Cancer Chemother Pharmacol 2000; 21: 374-5

Clinical Pharmacokinetics of Cyclophosphamide

Impact of Ondansetron?

Lorenz C, Eickhoff C, Baumann F et al. Krankenhauspharmazie 2000; 21: 374-5

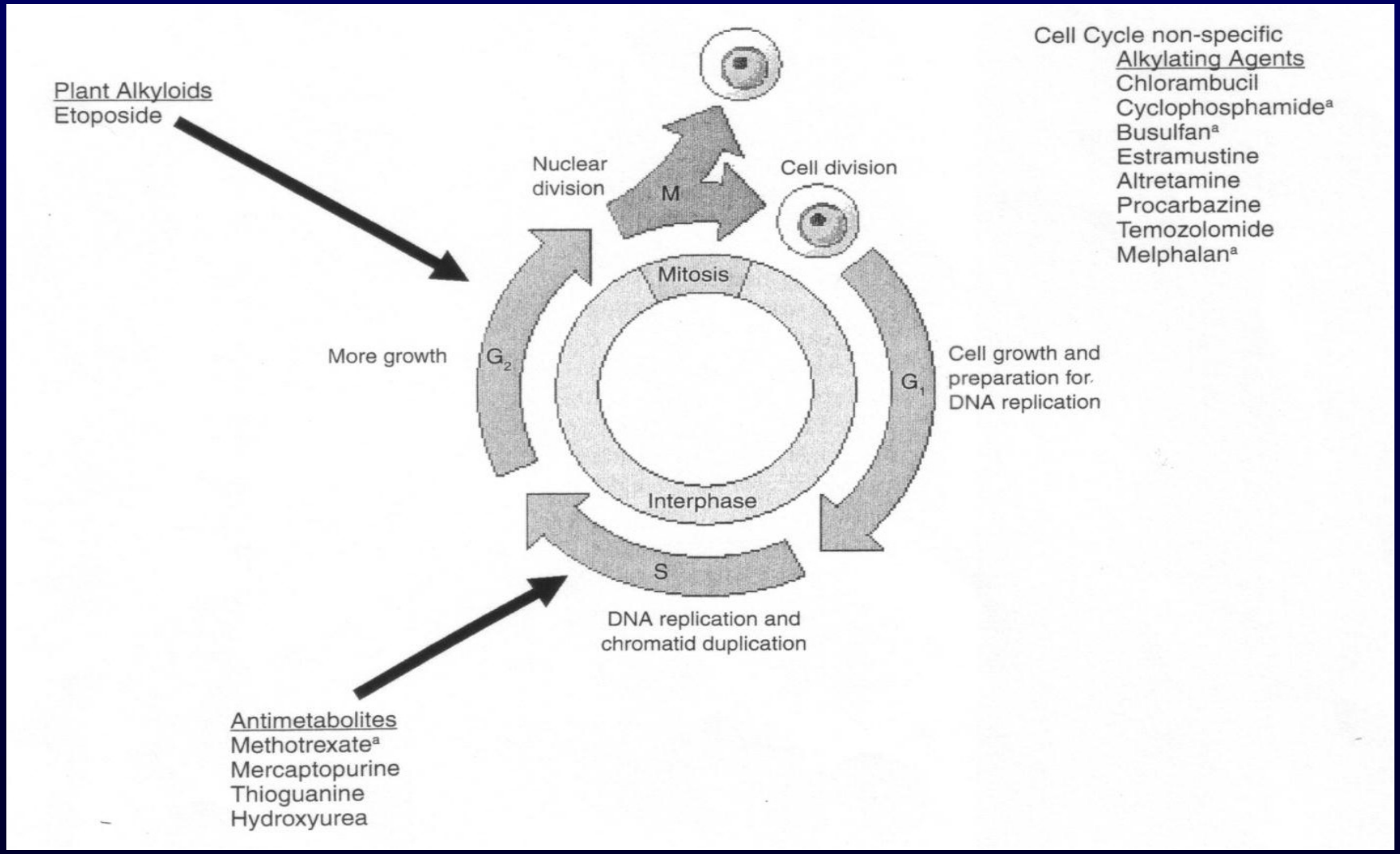
	With Ondansetron	Without Ondansetron
AUC (4-Hydroxy-Cyclophosphamide)	6,6± 2,3	6,1 ± 2,7
AUC (Carboxy-phosphamide)	19,3 ± 4,7	17,2 ± 4,7
t½ (4-Hydroxy-Cyclophosphamide) [h]	7,3 ± 2,1	8,3 ± 3,3

Conclusion:

Ondansetron has no impact on the clinical PK of cyclophosphamide

Pharmacodynamic interactions

In vitro – to – in vivo correlation?



Taxan-Platin-Combination Regimens

Sequence	Pharmakodynamic Outcome (Preclinic)
Paclitaxel→ 24h→Cisplatin **versus** **Cisplatin → Paclitaxel**	**Additive to synergistic effect in human gastric & Ovarian-Ca.-celllines** **Severe antagonistic effects**
Cisplatin → Paclitaxel	**Cisplatin-assoz. KHC-Gene damage with the consequence that Paclitaxel-assoc. Cytotoxicity was inhibited**
Cisplatin → Docetaxel	**Inhibition of Docetaxel-assoc. Apoptosis**
Nedaplatin/Paclitaxel od. **Nedaplatin → Paclitaxel** **versus** **Paclitaxel → Nedaplatin**	**Pretreatment with Nedaplatin resulted in absence of Taxane-induced apoptosis**
Carboplatin/Paclitaxel od. **Carboplatin → Paclitaxel** **Versus** **Paclitaxel → Carboplatin**	**Antagonistic interaction (Inhibition of Paclitaxel-assoc. IkappaB-alpha-Degradation and bcl-2-Phosphorylation** **No antagonism**

Praxisrelevante Interaktionen & Supportivtherapie

- Distinguish the spectrum and severity of side-effects between cytotoxic drugs and targeted therapy
- Consider the potential role of novel supportive strategies (individual decision *versus* regular use)
- Oral anticancer drugs need at least the same time for patient instruction compared to IV drugs
- The extent of drug interaction is dependent on the potency of the concomitantly used inhibiting or inducing agent – and my be life-threatening
- Interprete case reports reporting drug IA with caution
- Preclinical data indicate that the role of optimized drug sequences may be currently underestimated