Cisplatin alone and in combination with other drugs

- how do drugs affect each other and the patient?

Pharmacokinetics of Cisplatin

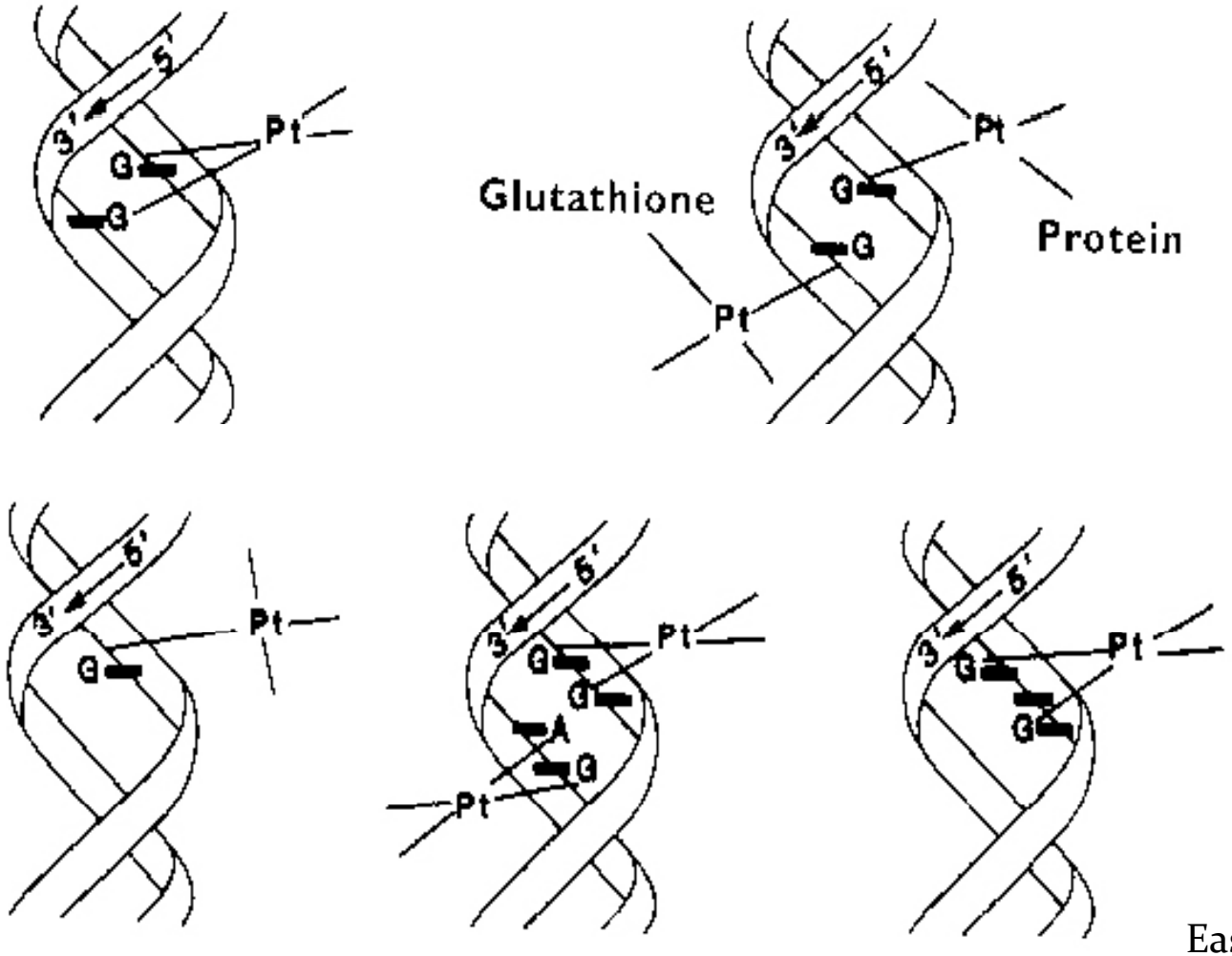
- After i.v. Infusion Cisplatin shows a biphasic elimination
- 4 hours after the injection, 90% of the drug is bound to serum proteins
- It accumulates mainly in the kidney, liver, uterus and ovaries
- Cisplatin can still be the detected in the tissues 4 months after the treatment

Schellers 2005, Merrin 1977

Pharmacodynamics of Cisplatin

- Accurate mechanism of action is still not clear
- An Aquo-complex is generated by nucleophilic substitution of Cl moieties with water molecules
- The product is positively charged

- This complex has a large affinity to nuleophile areas of the DNA
- Result: interstrand-, intrastrand crosslink, DNA-protein crosslinks and intereaktion with individual bases
- The highest frequency of cross-links is at GG sequences (N-7 position of Guanine shows highest nucleophilicity)



Eastman 1999

These reactions finally lead to disruption of the transcription, of the replication and finally inducing apoptosis

Cisplatin toxicity

Side Effects

- Nephrotoxicity
- Further adverse reactions:

  Ototoxity

  Neuropathy

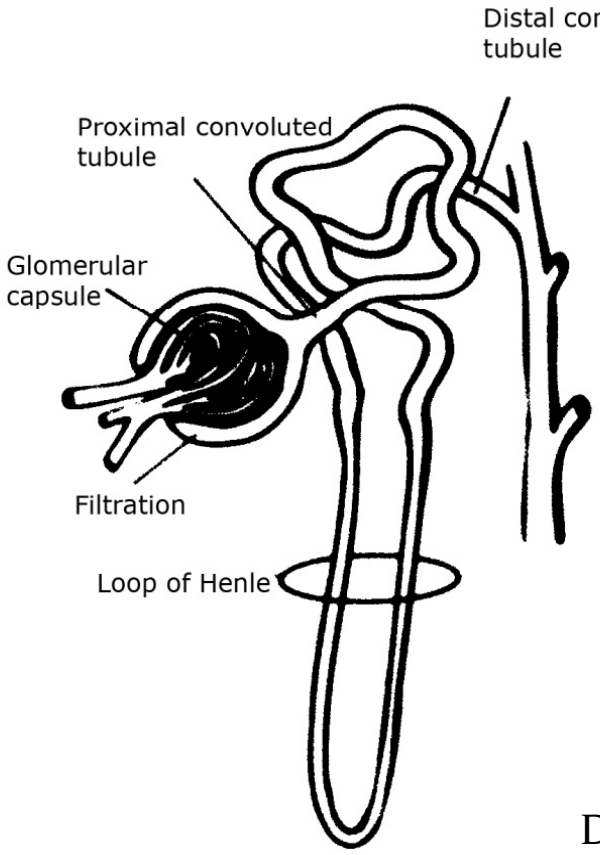
  Myelosuppresion

  Nausea and Emesis

Nephrotoxicity

- Renal damages appear as early as after the first Cisplatin injection

- Cisplatin accumulates in segment S3 of proximal tubule



Dipiro 1996

Nephrotoxicity

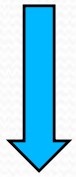
- Large doses of Cisplatin cause kidney damages due to the induction of apoptosis, smaller ones due to triggering necrosis
- During the apoptosis process, it comes to an activation of one cystein family, so called caspases, especially of caspase-3 and caspase-9

  These enzymes catalyse DNA fragmentation - cell death

Lau 1999

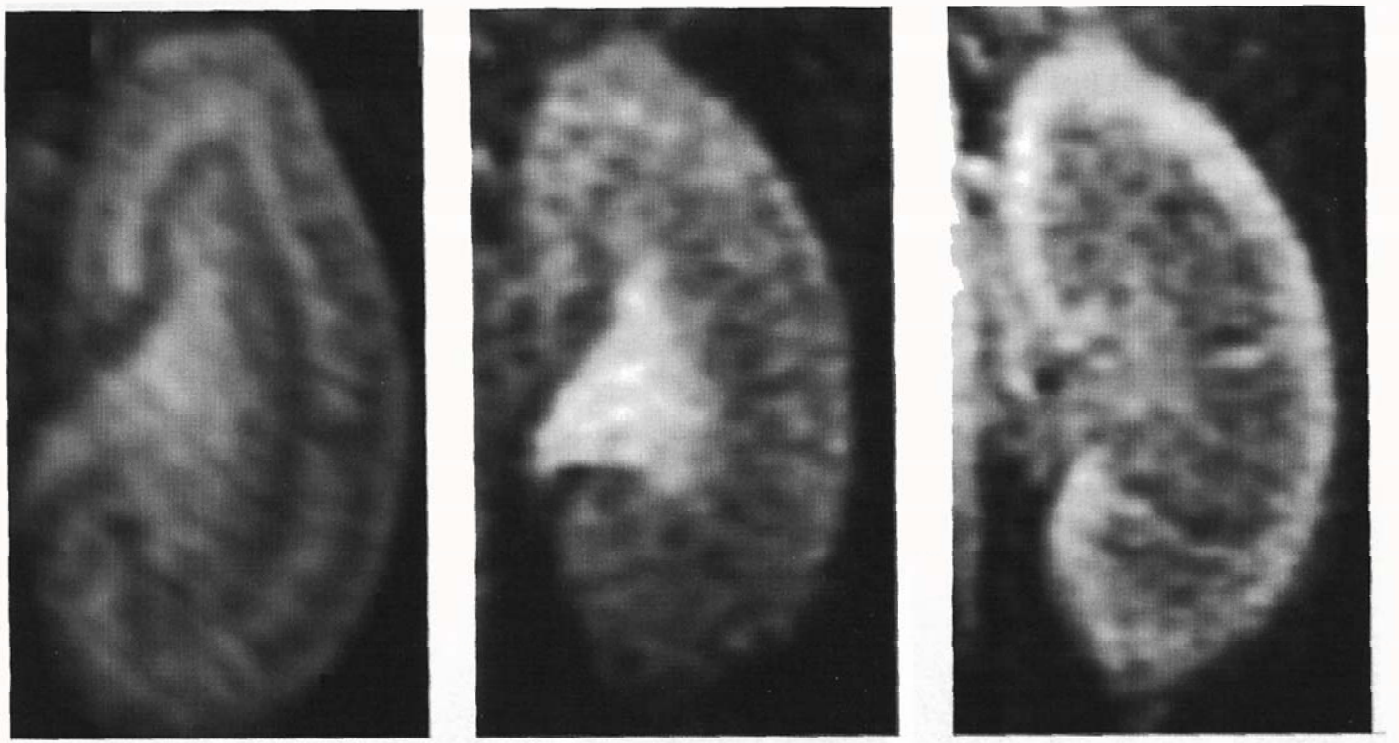
Consequences:

- Embossment of tubule epithelial layer
- Variation of the epithelial cells in size and form
- Thinning or dissapearing of ciliated border



Widening of tubule volume and degeneration of the tubule basal membran

Schwarz 2001



Dagher 2003

- In this situation, any presence of any other nephrotoxic drug could increase toxicity
- Any accumulation of such drugs could further constrict renal function

Drug	% excreted unchanged	Drug	% excreted unchanged
ANALGETICS		**ANTIBIOTICS**	
Acetaminophen	-	Aztreonam	75
Ass	60	Ampicillin	30
Diclofenac	1	Cefotaxim	60
Diflunisal	3	Cefpodoxime	30
Indomethacin	30	Cilastin	60
Ketorolac	30	Gentamicin	95
Piroxicam	10	Nitrofurantoin	30
ACE-Inhibitors		Tazobactam	65
Benazepril	20	**ANTIDIABETICS**	
Enalapril	43	Glyburide	50
Lisinopril	80	Insuline	50
Ramipril	10	Gliclazide	20
DIURETICS		Metformin	90
Amiloride	50	**ANTIFUNGALS**	
Ethacrinic acid	20	Amphotericin B	1
Thiazide	90	Fluconazole	70
Spironolactone	20	Itraconazole	35

Aronoff 1999

Forced diuresis

- Cvitkovic und collegues tested first in dogs, later in humans too, cisplatin treatment combined with forced hydratation
- Patients with highest hydratation rate showed lowest renal damage
- Sufficient administration of fluid assures quick passage of the toxic substance through the area of risk in the kidney
- Faster passage = lower risk of kidney damage

Case report

Objective Data

- Mr. KH : 63 years old
  weight 105 kg
  height 1,72m
- Anamnesis: Arteriole Hypertension
  Diabetes mellitus Type II - no obligatory insulin treatment
  Hernia inguinalis - operation as a child

Subjective Data

- Mr. HK suffered from a steady vesicle pain
- When he found blood in his urine, he was seaking for medical assistance
- A transurethral resection had to be carried out which detected a solid tumor G3, responding to Urethra carcinoma high grade
- Histological data showed infiltration of the tumor into the smooth muscle

- Chemotherapy schedule (Protocol Gemcitabine/Cisplatin):

  Day 1: Gemcitabinhydrochlorid 1000mg/m²

  Day 2: Cisplatin 70 mg/m²

  Day 3: Gemcitabinhydrochlorid 1000mg/m²

  Day 4: Gemcitabinhydrochlorid 1000mg/m²

- During his hospital stay, the patient fell into Status febrile with 38,5° C
- Antibiotic therapy started with Piperacillin/Tazobactam
- The urin culture examination showed the presence of MRSA
- Treatment continued with Oxazolidinon

Medication

Esomeprazol Tbl 40mg	1-0-1
Metformin Tbl 850mg	0-0-1
Lisinopril/HCT Tbl	1-0-0
Paracetamol (Acetaminophen) Tbl 500mg	1-1-1
Oxazolidinon Tbl 400mg	1-0-1
Granisetron Tbl 2mg	1-0-0
Metoclopramid gtt	3x20
Darbepoetin 500µm	q3w

Date	22/12	04/01	12/01	05/02	15/02	15/03	29/03	Reference Range
Sodium	139	141	142	145		136	142	135 - 150 mmol/l
Potassium	3.5	3.5	*3,3	3.7		3.5	*3,4	3,5 - 5,5 mmol/l
Magnesium							*0,68	0,7 - 1,0 mmol/l
Phosphate		0.96	*0,77					0,8 - 1,6mmol/l
Carbamide	*25,58	23.45	12.59	12.2	16.98	*31,3	24.11	6 - 25mg/dl
Uric acid	*7,4	5.9	6	6.4	*7,4	*7,3	*7,2	2,5 - 6mg/dl
Creatinine	*1,75	*1,55	*1,45	*1,38	*1,47	*1,49	*1,32	0,7 - 1,2 mmol/dl
CrCl	63.92	72.16	77.14	81.05	76.09	75.07	84.7	60ml/min/1,7m^2

Cause:

- Disadvantage of the Cock Croft Gault Formula

$$CrCl = \frac{(140 - age) \times BW}{72 \times S_{cr}} \times 0{,}85 \text{ (if female)}$$

CrCl = creatinine clearance (ml/min)
Age = years
BW = body weight in kg
S_{cr} = serum creatinine (mg/dl)

not representative for obese patients!

- Mr. HK has a BMI of 35,5
- The renal function is even more impaired than lab values actually reflect
- Therefore chemo was changed:
  Cisplatin was replaced by Carboplatin
- After three cycles febrile neutropenia with elevated CRP was diagnosed
- Treatment with Filgrastim

Antibiotic treatment

- Piperacillin/Tazobactam started
- High amount of parent compound can be found in the urine, the rest is eliminated as inactive metabolites by the kidney

Halstenson 1994

- Due to rapid switch to Oxazolidinon, cumulation could be avoided
- Total clearence of Oxazolidinon doesn't change with decreased renal function

Brier 2003

Hypertension treatment

- To treat hypertension, the patient has got a combination of lisinopril and HCT
- There are a large number of reports describing lisinopril accumulation in the kidney even at low doses
- → Mr. KH got his medicine once daily
- No cumulation could appear

- BRILLIANT Study showed that ACE-inhibitors compared to Ca-channel blockers induce decrease of Microalbuminuria
- The patient's lab data indicated that he had proteins in the urine

	27.02.2007	references
ph/U	6	5-9
nitrate/U	neg	0-10/ml
leuco/U	500	neg
protein/U	30	neg
glucose/U	neg	neg
keton/U	neg	neg
bilirubin/U	neg	neg
blood/U	20	neg

- EUCLID study reports a decelerating progression of renal insufficiency even for patients with albuminuria and a protective effect of lisinopril for patients with renal insuffiency

Lisinopril - a good choice!

- Hypertensive patients often need more than just one drug for appropriate regulation of blood pressure
- The ALLHAT study reports no superior effect of lisinopril in diabetic patients compared to thiazide diuretics
- Mr. KH got a combination medicine with lisinopril/HCT

- Thiazide diuretics operate by blocking the transport system in the proximal tubule
- Decreased renal function could result in a prolonged half-life of the drug
- Since cisplatin acts at the same place, it could come to additive toxicity

Niemeyer 1983

- Recently reports of prolonged neutropenia with HTC in cisplatin patients

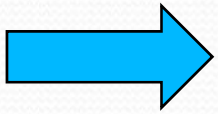
Diabetes

- Treated with metformin
- BMI of 35,5 - adiposity group II
- Indicated for obese patients after diet has failed

- UKPDS study: metformin reduces the possibility of diabetes related complications

first choice!

- Metformine almost not metabolised - unchanged renal elimination
- At chronic renal impairment not recommended
- Renal insufficiency increases metformine accumulation and decreases renal elimination of lactates

 life-threating acidosis

Harrower 1996

Date	12/01	31/01	05/01	15/02	15/03	29/03	Reference Range
Glucose		85			*124	*138	50 – 110 mg/dl
Bilirubin tot.	0.22		0.3	0.27	0.41	0.17	0,1 - 1,0 mg/dl
PankreasAmylase							17 – 115 U/l
Lipase							13 – 60 U/l
Cholinesterase						6.49	5,4 - 13,2 kU/l
AP	84		94	85	*176	100	35 – 105 U/l
GOT	27		38	35	30	22	0 - 35 U/l
GPT	22		43	34	*59	29	0 - 35 U/l
gGT	53		*131	*98		*83	0 - 40 U/l
LDH	185		*280	*275	*252	181	135 - 250U/l

Cisplatin

+ ACE-blocker/Diuretic

+ Metformine!!!!

→ Change antidiabetic drug!

Proposal:

sulfonylurea drug - low percentage of renal elimination

e.g. Glyquidone (just 5%)

- For treatment of pain, Mr. HK got paracetamol (acetaminophen)
- Metabolised in the liver via conjugation with glucuronic acid and sulfate
- More than 90% of therapeutical dose ends up as metabolites in the urine

- Patients with renal impairment have a limited ability to excrete all polar metabolites and with repeated application, accumulation of paracetamol metabolites must be expected
- Large single doses of paracetamol may cause renal impairment, too

- Paracetamol-induced kidney damages result from apoptosis of proximal tubule cells
- The cell death follows by activation of enzymes caspase 3 and 9

Same mechanism as cisplatin!!!

Lorz 2004

→ **stop medication immediately!**

- Since all NSAR are also contraindicated at renal insufficiency, metamizole or weak opoid could be recommended

Conclusion

- Apparent nephropathy can be the outcome of coadministration of drugs which are regarded as “safe” when they are given alone

- Be careful with the following drugs…

ANALGETICS
Acetaminophen
Ass
Diclofenac
Diflunisal
Indomethacin
Ketorolac
Piroxicam

ACE-Inhibitors
Benazepril
Enalapril
Lisinopril
Ramipril

DIURETICS
Amiloride
Chlorthalidone
Ethacrynic acid
Thiazide

ANTIBIOTICS
Amikacin
Ampicillin
Cefpodoxime
Cefotaxim
Gentamicin
Nitrofurantoin
Teicoplanin
Tobramycin

ANTIDIABETICS
Glyburide
Insuline
Gliclazide
Metformin

ANTIFUNGALS
Amphotericin B
Fluconazole
Itraconazole

BETA-BLOCKERS
Atenolol
Bisoprolol
Carteolol
Nadolol
Sotalol

ANTIVIRAL
Amantadine
Didanosid
Foscarnet
Ganciclovir
Ribavirin

ANTIHISTAMINES
Cimetidine
Cetirizine
Famotidine
Nizatidine
Ranitidine

ARTHRITIS AGENTS
Allopurinol
Auranofin
Colchicine
Penicillamine
Probenecid

BRONCHODILATORS
Albuterol
Dyphilline
Terbutaline

HYPOLIPIDEMIC
Clofibrate
Bezafibrate
Nicotinic acid

NEUROMUSCULAR
Gallamine
Neostigmine
Tubocurarine

Aronoff 1999, Deuber 2001

Thank you for your attention!