The right dose to the right patient – chemotherapy adaption in specific situations

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ausgezeichnet und gefördert
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Overview

- treatment of obese patients
- treatment in renal insufficiency and dialysis pts
- liver function and dosing
- include some dosing aspects for targeted agents

The problem (1)

male, 26 years
BW 145 kg, 1.92 m hight → BSA: > 2.5 m2

Diagnosis: metastatic testicular cancer with pulmonary lesions
Curative chemotherapy planned

Dosing of chemotherapy (PEB)

P cisplatinum	-	renal, oto- and neurotoxicity increased?
E etoposide	-	myelotoxicity, risk for secundary leukemia?
B bleomycine	-	more pulmonary toxicity?

Introduction & Context

- **Population: Adult obese patients with cancer**
  - Greater than 60% of adults in US have body mass index (BMI) greater than 25 and are considered overweight or obese

- Chemotherapy dosing is based on patient's estimated BSA using several formulae which include the body weight

- Studies confirm importance of full weight-based doses of cytotoxic chemotherapy (at least in the curative setting)

  - Up to 40% of obese pts receive limited doses not based on actual body weight
  - Chemotherapy dosing limited at 2m2 BSA

Guideline Methodology: Systematic Review

- **An Expert Panel reviewed relevant medical literature**
- Database searched:
  - MEDLINE
  - Cochrane Collaboration Library
- Data parameters:
  - January 1966 – October 2010
- Ongoing clinical trials monitored
  - The National Cancer Institute's (NCI) database of clinical trials
  - National Library of Medicine's clinicaltrials.gov

J.J. Griggs, April JCO 2012

Does weight-based dosing increase toxicity?

Recommendation #1.1:

- **Use actual body weight to calculate cytotoxic chemotherapy dose regardless of obesity status**
- **No evidence that short- or long-term toxicity is increased with full weight-based doses**
- In patients receiving chemotherapy dosed on the basis of actual body weight, **myelosupression is the same or less pronounced in obese patients** with cancer than in non-obese patients

Is efficacy compromised with lower than weight-based dosing?

Recommendation #2.1:

- Use weight-based doses especially in curative setting
- **Reduced doses may result in poorer disease-free and overall survival rates**
  - **Supporting data in patients with breast cancer**
  - **Dose-response relationship exists for many other responsive malignancies e.g., lung and gynecologic cancers**
  - Most data from treatment of early-stage disease
- Data in advanced disease (palliative) setting are limited

Dose capping in MRC colorectal cancer trials

4856 pts. in MRC colorectal cancer trials:

- 2002 (45%) normal weight
- 1774 (34%) overweight
- 880 (18%) obese

- Reduced doses:
  - normal weight 6%,
  - overweight 17%,
  - obese 55% (sig)

- Toxicity: normal weight 21%, overweight 20%, obese 17%

- **Toxicity in obese pts: full dose 17%, reduced dose 16%**

- Survival normal versus reduced dose **HR 1.16**

Chambers P, et al. Ann Oncol 23, 2012

Is a **fixed dose ever justified** for obese patients?

Recommendation #4.1:

- **Consider fixed dosing only with selected cytotoxics**
  - **Examples: carboplatin -- > use GFR based dosing**
  - **Bleomycin always fixed dose**
  - **Oxaliplatin ? Limit at 2m2 ?**
- **Due to neurotoxicity concerns, cap vincristine at maximum of 2.0 when used as single agent or part of CHOP* or CVP****

* CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone

** CVP = cyclophosphamide, vincristine, prednisone

How should BSA be calculated?

Recommendation #5.1:

- **Calculate BSA with any standard formula**
- No evidence supporting one formula for calculating body surface area over another

Common Formulae

BSA

- **Boyd Formula**
  - BSA (m^2) = 0.0003207 x Ht (cm)$^{0.3}$ x weight (g) $^{(0.7285-(0.0188 \times LOG_{10} weght(g)))}$
- **DuBois and DuBois Formula**
  - BMS (m^2) = Wt(Kg)$^{0.425}$x Ht(cm)$^{0.725}$ x 0.007184

- The full guideline, data supplements, patient guide, a dosing table, podcasts, FAQs, and other resources are available at www.asco.org/guidelines/wbd
- The patient guide is also available at http://www.cancer.net

The problem (2)

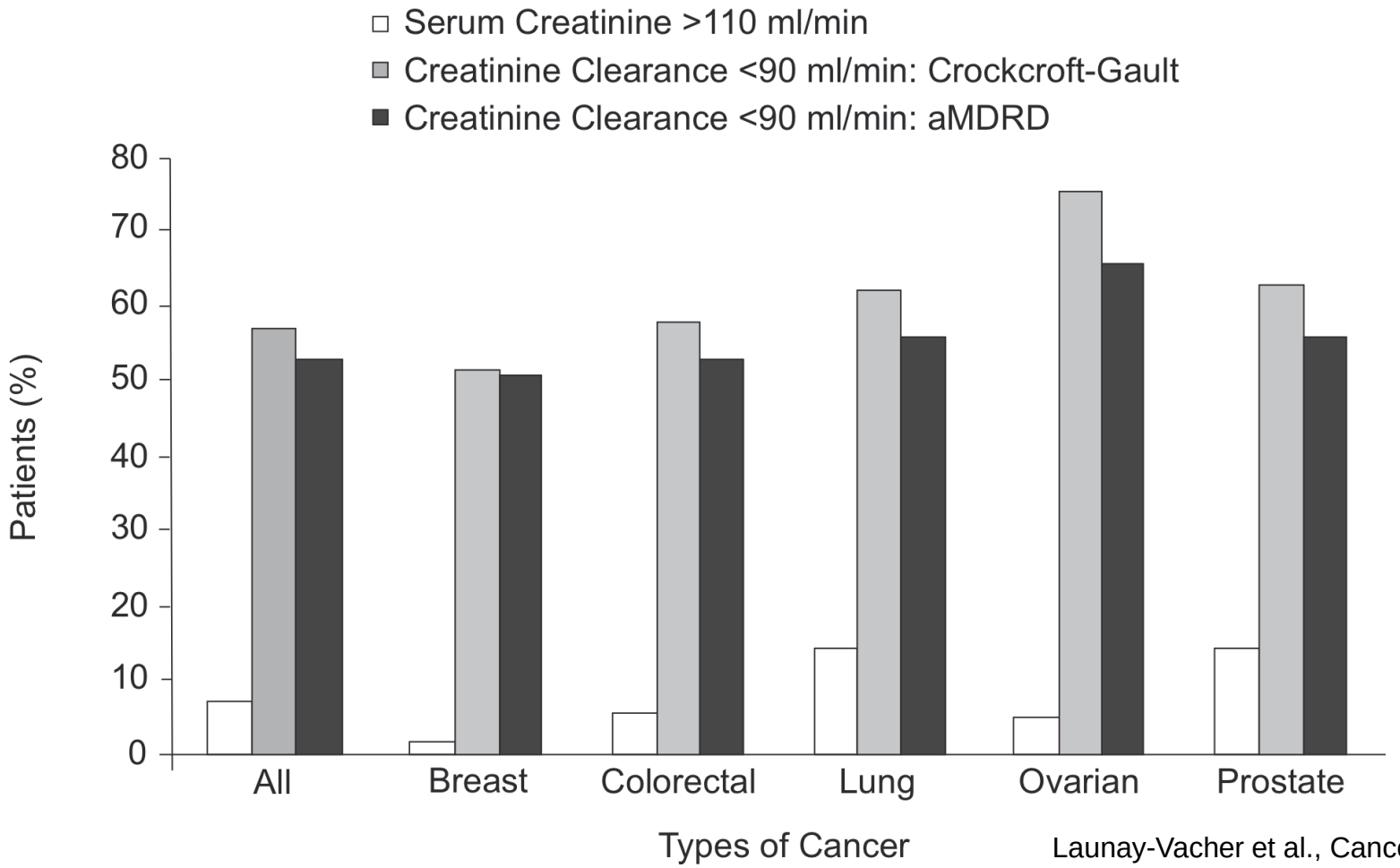
female patient 69 years;
metastatic colorectal cancer (liver, lung, lymphatic nodes)
GFR 35 ml/min, no known renal disease

Dosing of chemotherapy (XELOX planned)

Capecitabine	-	increased toxicity due to reduced clearance?
Oxaliplatin	-	dose reduction necessary for renal toxicity or due to potential increase of side effects?

Renal function and chemotherapy

French study of 4684 pts presenting at 15 cancer centers in 2004
52 % had decreassed renal fuction according to MDRD formula,
half were treated with drugs requiring dose adaption based on renal fuction



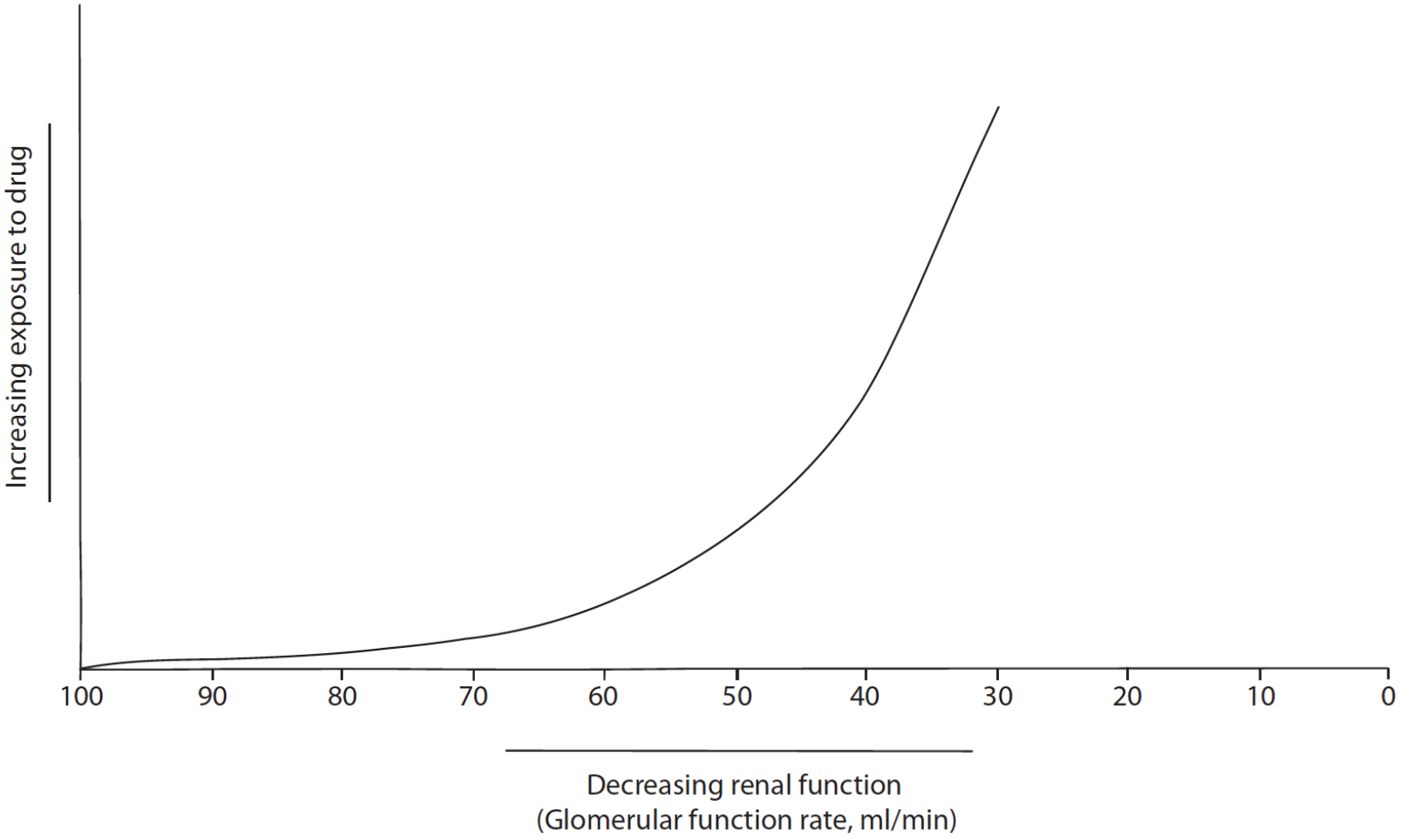
Launay-Vacher et al., Cancer, 2007

Stages of chronic renal insufficiency

Stage	Description GFR	(mL/min/1.73 m2)
0	Patients with risk factors for developing kidney disease: patients should be monitored	More than 90
1	Kidney damage and normal GFR	More than 90
2	Kidney damage and mild decrease in GFR	60–89
3	**Moderate decrease in GFR**	**30–59**
4	**Severe decrease in GFR**	**15–29**
5	**Kidney failure (dialysis or kidney transplant needed)**	**Less than 15**

Renal function and drug exposure

Decreased renal clearance increases exposure to all drugs not only cytotoxics



Aapro et al., Cancer Treatment Reviews, 2011

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Nephrotoxic Cytotoxics

Drug	Renal Toxicity	Mechanism	Preventive Strategies	Treatment
Cisplatin	ArF; tubular damage; renal concentration defect; polyuria; hypomagnesemia; rarely HUs	Toxic damage to the s3 segment of proximal Tubule, loop of Henle, and distal tubules	volume infusion, amifostine	Avoid further use; volume infusion; magnesium repletion; dialysis for uremia
Ifosfamide	subclinical tubular damage in most Patients; severe electrolyte depletion; nephrogenic diabetes insipidus;	Proximal tubular damage by metabolites such as chloracetaldehyde; total dose-related toxicity	Mesna (questionable benefit); avoid concomitant cisplatin	Bicarbonate; phosphate; electrolyte repletion
Mitomycin C	TTP and HUs often presents as ArF	Thrombotic microangiopathic lesions; glomerular infarction	No established preventive measures	Plasmapheresis; Staphylococcus A column immunoadsorption
Methotrexate	renal failure with high dose therapy (1.8%)	Precipitation of methotrexate and 7-hydroxymethotrexate into renal tubules	volume infusion; alkalinization with sodium bicarbonate; leucovorin rescue	supportive measures; Dialysis; carboxypeptidase-G2

Sahni et al., Nature Review Nephrology, 2009

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Nephrotoxic Cytotoxics

Drug	% dose excreted in urine	90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min
Cisplatin	90	50 to 120 mg/m2 every 3 to 6 weeks	Not recommended, however if unavoidable an appropriate dose should be used: 25 to 60 mg/m2 every 3 to 6 weeks		Not recommended,
Carboplatin	95	Adjust according to patient using a formula such as the Calvert formula.			
Oxaliplatin	54	85 or 100 mg/m2 every 2 weeks, or 130 mg/m2 every 3 weeks			Contraindicated
Methotrexate	55-88	30 to 50 mg/m2	24 to 40 mg/m2	15 to 25 mg/m2	Contraindicated
Ifosfamide	45	dose/day: 1.5 to 3 g/m2; dose/cycle: 5 to 10 g/m2			dose/day: 1.13 to 2.25 g/m2 dose/cycle: 3.75 to 7.5 g/m2

Lichtmann et al., EUROPEAN JOURNAL OF CANCER, *2007*

Renal dosing of carboplatin

Carboplatin dosing:

How to choose the target AUC?

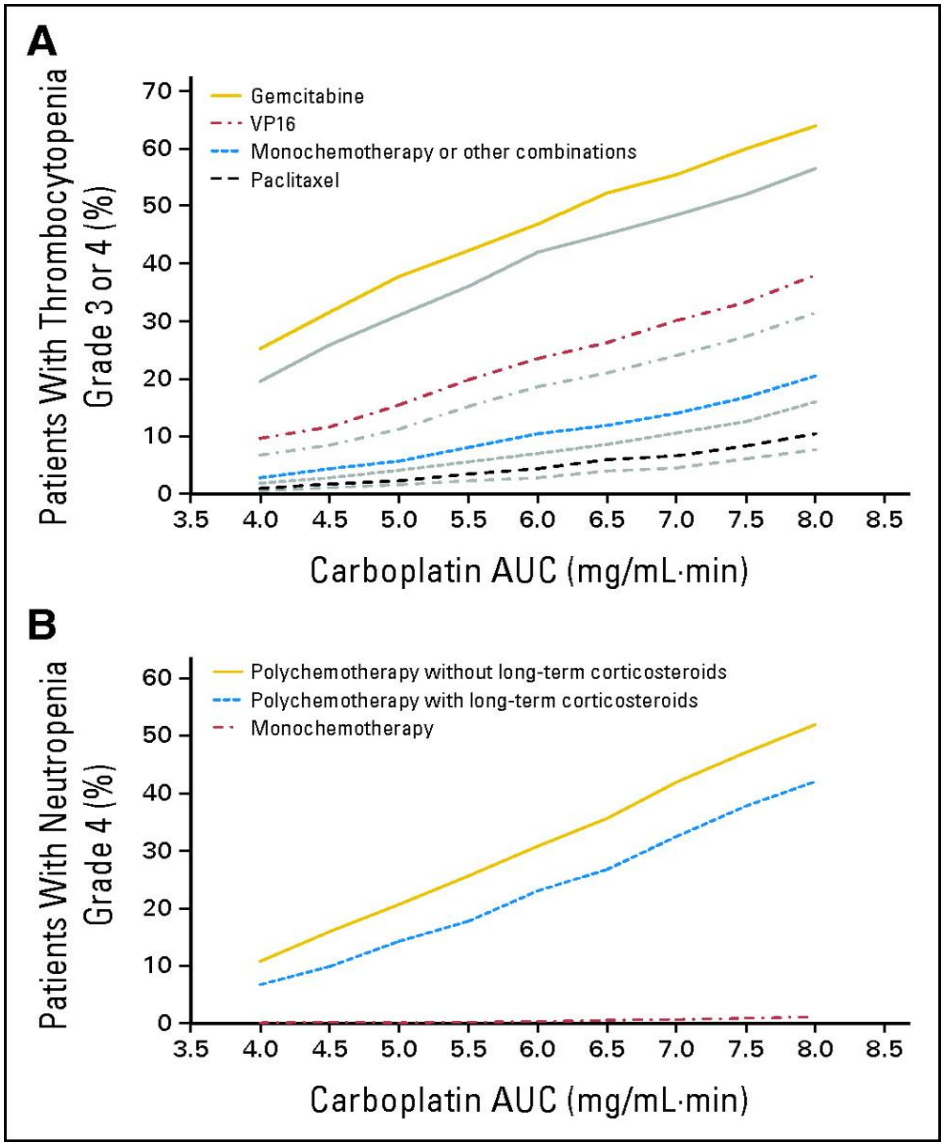
$\Rightarrow$ Estimated hematotoxicity (neutropenia, thrombocytpenia)

- 383 pts with carboplatin - based therapies
  PK-PD model correlated to hematoxicity

$\Rightarrow$ chosen combination effects risk of grade 3/4 thrombopenia
(low risk with paclitaxel, higher risk with gemcitabine)

A. Schmitt et al, JCO 2010

Simulated percentage of patients experiencing hematotoxicity according to the final models



Thrombocytopenia grade 3 or 4.

Gold, red, and blue indicate previous chemotherapy; gray indicates no chemotherapy.

Neutropenia grade 4.

VP16, etoposide;
AUC, area under the curve.

Schmitt A et al. JCO 2010;28:4568-4574

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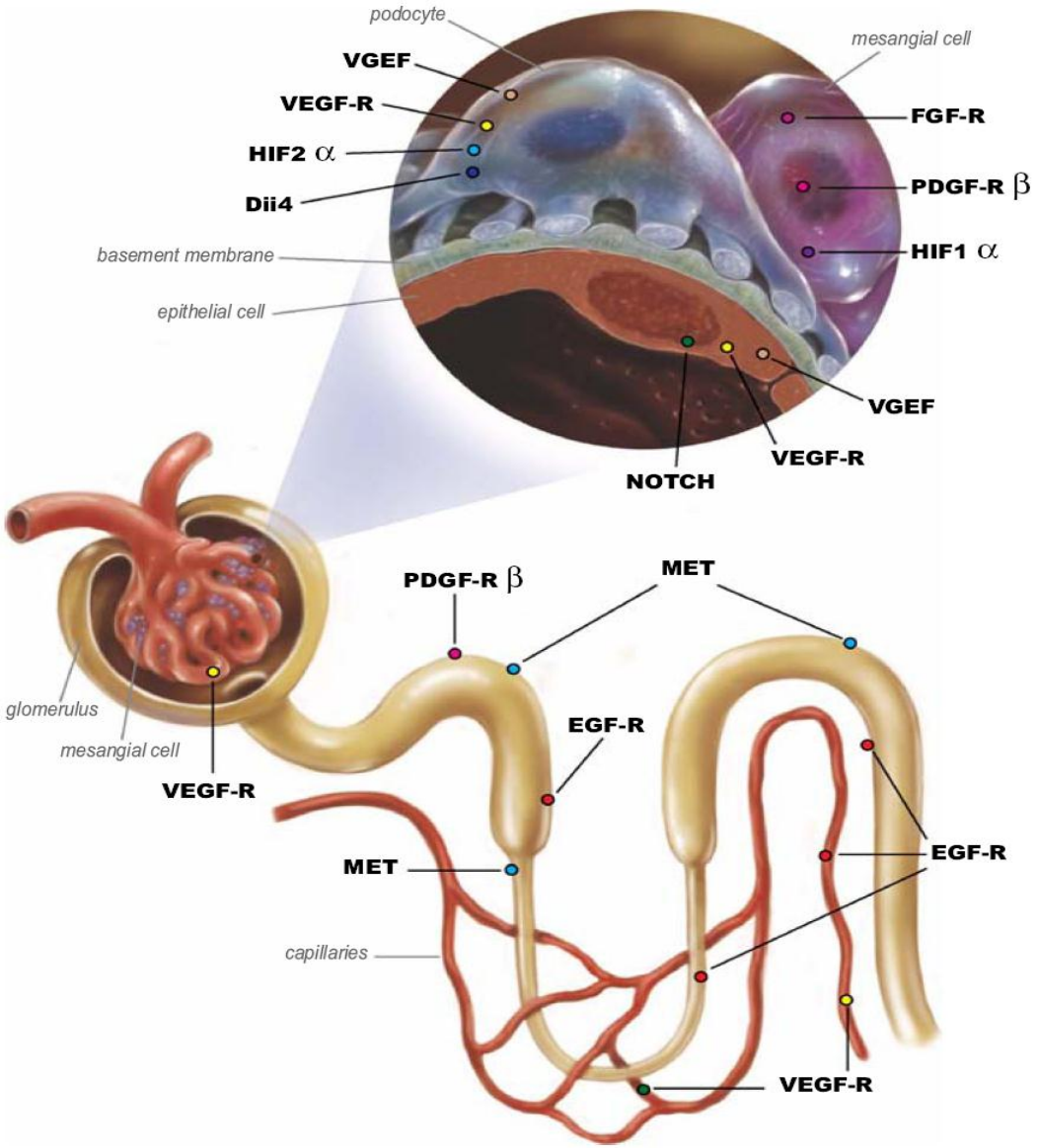
Targeted agents can effect renal function



Kelly et al., 2009

The special case:Chemotherapy in dialyses pts

- Dose reduction to avoid side effects - not to protect the kidneys
- the time between chemotherapy and dialysis is crucial

Need for dosage adjustment in hemodialysis

Drug	Patients according to Launay-Vacher et al.	Patients according to Lichtman et al.
5-FU	**No**	**No**
Capecitabine	No data	No data
Carboplatin	**Yes**	**Yes**
Cisplatin	**Yes**	**Yes**
Cyclophosphamide	Yes	Not mentioned in the recommendations
Docetaxel	No data	No data
Doxorubicin	**No**	**No data**
Epirubicin	**No data**	**No**
Etoposide	**Yes**	**Yes**
Gemcitabine	No	No data
Irinotecan	No data	No data
Methotrexate	No data	No data
Oxaliplatin	No data	No data
Paclitaxel	**No**	**No**
Vinorelbine i.v.	Yes	No data

Janus et al., Ann Oncol, 2010

The problem (3)

58 years, male
colorectal cancer with liver metastases, k-ras wildtype
Immediate response to chemotherapy required due to very advanced disease
total bilirubin 2,5 mg/dl, transaminases 200-300 U/l

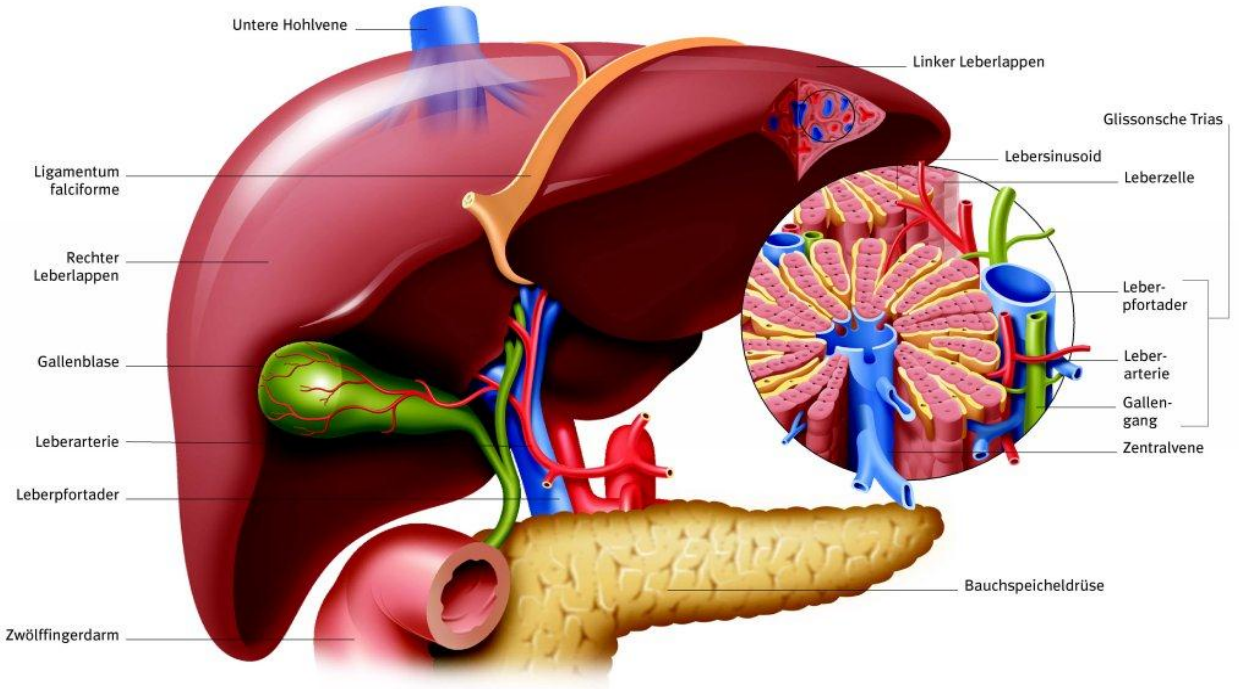
Dosing of chemotherapy FOLFIRI + Cetuximab

5FU	-	reduction necessary ?
Irinotecan	-	at all possible despite brb ↑ ?
Cetuximab	-	no problem ?

Pharmakological tasks of the liver

- Absorption: 1st-pass Effekt ↑
- Distribution ↑: Proteinsynthesis ↓ → proteinbinding ↓
- Metabolismus ↓: CYP, NAT, ST, GST
- Elimination ↓: UGT, MDR1 (p-glykoproteine)

Drug-exposure↑



Paclitaxel

Up to a bilirubin of 80 µmol/L dose adaption can follow the following recommendations:

				Initial paclitaxel dose (mg/m²)	
Cohort	*ALT/AST*	*Bilirubin*	*Dose level*	*Predefined*	*Model-derived recommendation*
I	< 2.6 x ULN	≤ 1.25 x ULN	0	175	*
II	2.6-10 x ULN	≤ 1.25 x ULN	0	175	175 ¶
III	< 10 x ULN	1.26-2.0 x ULN	0	175	115
IV	< 10 x ULN	2.1-3.5 x ULN	-1	135	100
V	< 10 x ULN	≥ 3.6-10 x ULN	-2	110	80

Joerger et al, Br J Clin Pharmacol 2007;64(5): 622-33.

AST or ALT	Serum-Bilirubin	Paclitaxel dose reduction	3-weekly dosing
>2-times ULN	<20µmol/L (1.5mg/dl)	-20%	135mg/m^2
<10-times ULN	>20µmol/L (1.5mg/dl)	-50%	90mg/m^2
>10-times ULN	>80µmol/L (5mg/dl)	**Not recommended**	

Gemcitabine

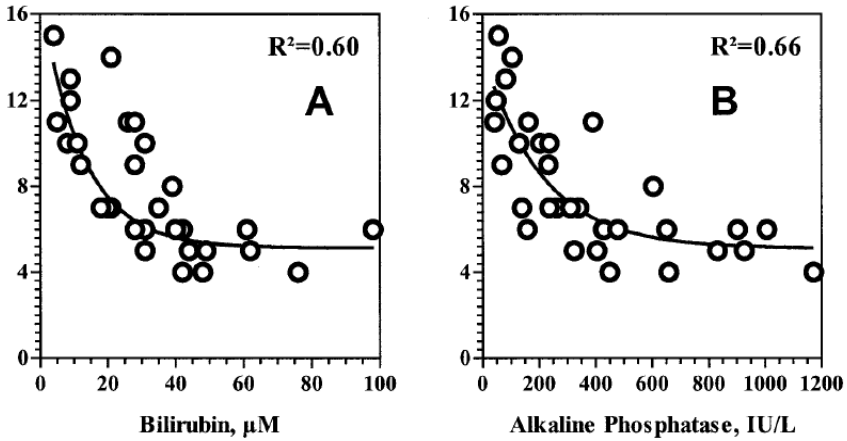
- Clinical study of pts with different severity of liver dysfunction
- Gemcitabine 1000mg/m^2 d1/8,
  Capecitabine 650mg/m^2 d1-15, q3w

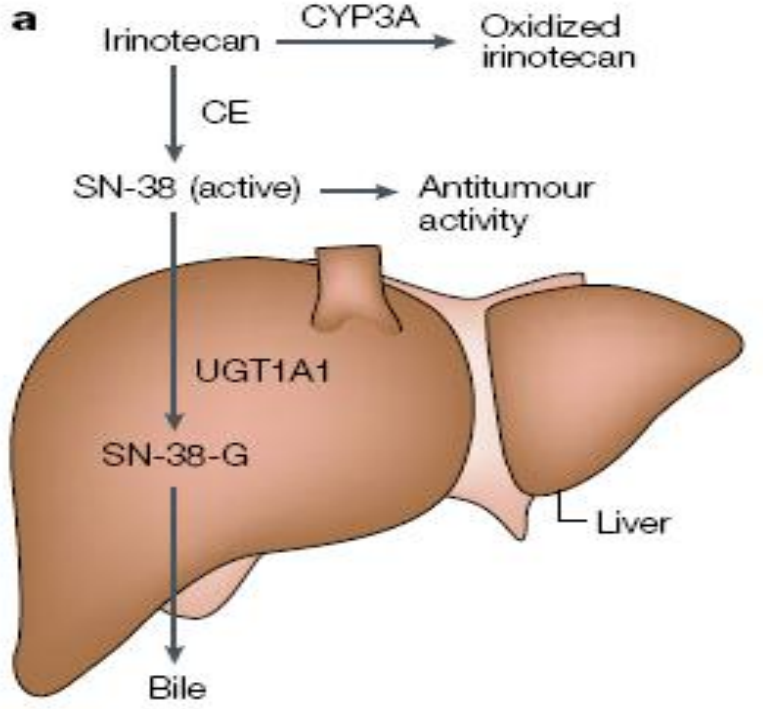
COHORT	Serum-Bilirubin (µmol/L)	ASAT/ALAT (U/L)
1	< ULN	≤ 2 times ULN
2	ULN to ≤ 30	≤ 10 times ULN
3	30 to ≤ 50	≤ 10 times ULN
4	50 to ≤ 80	≤ 10 times ULN

- Bilirubin 30-50 µmol/L → 20% dose reduction
- Bilirubin 50-80 µmol/L → 33% dose reduction

Irinotecan

- Clearance negatively correlated to bilirubin, AP[1]





- Dose recommendation:

		TOTAL SERUM-BILIRUBIN (µmol/L)		
Time	**Standard dose**	**1.5-3.0xULN**	**3.1-5.0xULN**	**1.5-3.0xULN + AST/ALT >5xULN**
3-weekly	**350mg/m²**	**200mg/m²**	**100mg/m²**	**Bili >5xULN → not recommended**
1-weekly	**125mg/m²**	**60mg/m²**	**50mg/m²**	**40mg/m²**

[1]Raymond et al, J Clin Oncol 2002;20: 4303-12.

Sorafenib

- orally applicable multi-tyrosinkinase inhibitor
- hepatic metabolisation via CYP3A4
- hepatic elimination via the bile fluid, particularly UGT1A9-mediated glucuronidation
- Recommendated dose recudtions[1]:
  - Bilirubin 1.5-3.0xULN, any AST → 200mg bid
  - Albumin <2.5mg/dL (any Bilirubin/AST) → 200mg qd
  - Bilirubin >3.0xULN → Sorafenib not tolerated

[1] *Miller et al, J Clin Oncol 2009(27): 1800-05*

Tyrosine kinase inhibitors and mTOR inhibitors

Drug	Child-Pugh A	Child-Pugh B	Child-Pugh C	References	Notes
Imatinib	400mg/d	400mg/d	**300mg/d**	Ramanathan, JCO 2008;26:563-9	**CYP3A4**
Erlotinib	75mg/d	75mg/d	**unknown**	Miller, JCO 2007;25:3055-60	
Gefitinib	250mg/d	250mg/d	250mg/d	Twelves, Proc Am Soc Clin Oncol 2002;21:abstr 339	
Sunitinib	50mg/d (4/2)	50mg/d (4/2)	**unknown**	Bello, Cancer Chemother Pharm 2010;66:699-707	
Sorafenib	400mg bid	**200mg bid or not at al**	**Not recommended**	Miller, JCO 2009;27:1800-5	
Lapatinib	1250mg/d	**unknown**	**unknown**	Medina, Clin Ther 2008;30:1426-47	
Temsirolimus	25mg/wk	25mg/wk	**10mg/wk**	Boni, Semin Oncol 2009;36(suppl):S18-25	
Everolimus	10mg/d	5gm/d	**unknown**	Kovarik, Clin Phrmacol Ther 2001;70:425-30	

Conclusion

Multiple situations in routine daily practice may require dose adaptation of chemotherapy and /or targeted agents

Most common situations are renal and hepatic insufficiency

Data on safety of dose modifications are limited, but careful action is always required

In contrast to dose reductions in the above situations, for obese patients no routine change of BSA - based chemotherapy dosing is required

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