SITUACIONES ESPECIALES EN CÁNCER DE PULMÓN

IV JORNADA GRUPO GIDO

Dr. Carlos Del Pozo

TRATAMIENTO ONCOLÓGICO EN EL PACIENTE CON INSUFICIENCIA RENAL

INSUFICIENCIA RENAL AGUDA

- **ALTERACIONES HIDROELECTROLÍTICAS**
  - Disminución volumen circulante eficaz
  - Hipercalcemia
- **FÁRMACOS**
  - AINES
  - Hipotensores. ATB
- **EXPLORACIONES RADIOLÓGICAS**
  - Contrastes.
  - Gadolinio

INSUFICIENCIA RENAL CRÓNICA

- **¿DEFINICIÓN?**

- **MEDIDAS DE FUNCIÓN RENAL**

MEDICIÓN FILTRADO GLOMERULAR

- **Marcador endógeno ideal:**
  - **Generación a ritmo constante.**
  - **Filtrado libre por el glomérulo.**
  - **No secreción ni reabsorción tubular.**
  - **No aclaramiento extrarenal.**

Aclaramiento de inulina. Isótopos

ESTIMACIÓN DEL FG

- **Creatinina plasmática.**
- **Aclaramiento de creatinina con orina de 24 horas.**
- **Ecuaciones derivadas de la creatinina.**
  - **Cockroft-Gault.**
  - **MDRD.**
  - **Otras (Jelliffe/ Wright).**
- **Cistatina.**

COCKROFT-GAULT

CrCl = (140 – Edad) x (Peso Kg) x (0.85 sí mujer) / Cr plasma (mg/dl) x 72

- **Nephron 1976. Requiere ajuste a Superficie Corporal (DuBois/ Mosteller)**
- **Favorita de los farmacólogos.**
- **Recomendada por la FDA.**
- **Sobreestima FG en obesos.**
- **Infraestima FG con función renal normal y en ancianos**
- **Abandonada progresivamente por nefrólogos y clínicos.**

MDRD. Modification of Diet in Renal Disease

- **Levey en 1999 (Ann Inter Med)**

MDRD-7

$170 \times Cr\ (mg/dl)^{-0.999} \times edad\ (años)^{-0.176} \times BUN\ (mg/dl)^{-0.170} \times Alb\ (gr/dl)^{0.318} \times (0.762\ si\ mujer\ y/o\ 1.180\ si\ raza\ negra)$

- **Levey en 2000 (J Am Soc Nephrol) (K/DOQI)**

MDRD-4 abreviada

$186 \times Cr^{-1.154} \times edad^{-0.203} \times (0.742\ si\ mujer) \times (1.210\ si\ raza\ negra)$

- **2005: MDRD-IDMS.**

- **2009: CKD-EPI. Chronic Kidney Disease Epidemiology Collaboration**

-. (KDIGO. 2013). SEN (2014).

mdrd.com

MDRD

- Cómodo, requiere sólo Crp, edad, sexo y raza.
- Se considera más precisa que Cockroft y CrCl (orina 24 hs)
- Adecuada estimación en sujetos con ERC (CrCl 15-60 ml/min)
- Infraestima FG cuando función renal es normal.
- En IMC extremas (<20 / > 35) ajustar (FG x SC/1.73 m^2)
- CKD-EPI mejora estimación FG a niveles > 60 ml/min/1,73m^2.

mdrd.com

ESTADIOS DE ERC. MDRD. CKD-EPI

- **Estadio 1……..FG > 90 ml/min/1.73 m^2SC**
- **Estadio 2……..FG: 60-89 ml/min/1.73 m^2SC**
- **Estadio 3……..FG: 30-59 ml/min/1.73 m^2SC**
  - **3a) FG entre 45 y 59 ml/min/1.73 m^2SC**
  - **3b) FG entre 30 y 45 ml/min/1.73 m^2SC**
- **Estadio 4……..FG: 15- 29 ml/min/1.73 m^2SC**
- **Estadio 5……..FG < 15 ml/min/1.73 m^2SC**

mdrd.com

EJEMPLOS

- **MDRD**
  - **Mujer. 60 años. Cr: 1.1 mg/dl**
  - **MDRD: 51 ml/min/1.73 m^2 SC (CKD-EPI: 55)**

  - **Hombre. 60 años. Cr: 1.1 mg/dl.**
  - **MDRD: 68 ml/min/1.73 CGm^2 SC (CKD-EPI: 73)**

- **MDRD**
  - **Mujer. 80 años. Cr: 1.1 mg/dl**
  - **MDRD: 48 ml/min/1.73 (CKD-EPI: 48)**

  - **Hombre. 80 años. Cr: 1.1 mg/dl.**
  - **MDRD: 64 ml/min/1.73 (CKD-EPI: 63)**

La prevalencia de Crp elevada en pacientes con cáncer es baja (10%)
La prevalencia de FG bajo es relativamente alta (50-53 %)

CISTATINA C

- **Es una proteína básica no glucosilada de bajo PM, sintetizada por todas las células nucleadas a velocidad estable.**
- **Se filtra libremente, se reabsorbe y cataboliza en TCP.**
- **Potencial sustituto de la Cr como marcador endógeno del FG.**

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

Lesley A. Inker, M.D., Christopher H. Schmid, Ph.D., Hocine Tighiouart, M.S., John H. Eckfeldt, M.D., Ph.D., Harold I. Feldman, M.D., Tom Greene, Ph.D., John W. Kusek, Ph.D., Jane Manzi, Ph.D., Frederick Van Lente, Ph.D., Yaping Lucy Zhang, M.S., Josef Coresh, M.D., Ph.D., and Andrew S. Levey, M.D., for the CKD-EPI Investigators*

N Engl J Med 367;1-20. 2012

NO USAR ECUACIONES SI:

- FRA
- Desnutrición
- Hepatopatía grave, ascitis
- Patología muscular. Amputados
- Dietas especiales: vegetarianas, ricas en creatina
- Fármacos que bloquean la secreción de creatinina

DOSIFICACIÓN / FICHA TÉCNICA FÁRMACOS

ADO	ERC leve FGe > 50	ERC moderada FGe = 30-50	ERC grave FGe < 30
Metformina	Sí	Sí (No en ficha técnica)	No
Pioglitazona	Sí	Sí	Sí
Repaglinida	Sí	Sí	Sí
Sulfonilureas	Sí	Sí	No
iDPP4	Sí	Sí	Sí
Acarbosa	Sí	Sí	No

A. Martinez Castelao y cols. Nefrología 2012; 32(4): 419-26

Cockroft-Gault
Aclaramiento de creatinina
Creatinina
Fórmula de Wright /Jelliffe

Tabla 1. Recomendación de ajuste de dosis de dabigatrán según la tasa de filtración glomerular estimada por diferentes fórmulas

Fórmula utilizada para estimar la TFG	Resultado	Unidades	Recomendación según ficha técnica
Cockcroft-Gault	31,3	ml/min	Indicado
MDRD-4v	28,6	ml/min/1,73 m²	Contraindicado
MDRD-4v corregido por superficie corporal	35,1	ml/min	Indicado
CKD-EPI	26,3	ml/min/1,73 m²	Contraindicado

Varón de 85 años de raza blanca, 180 cm de altura y 90 kg de peso, con creatinina en suero de 2,2 mg/dl. Superficie corporal estimada de 2,1 m².
TFG: tasa de filtración glomerular.

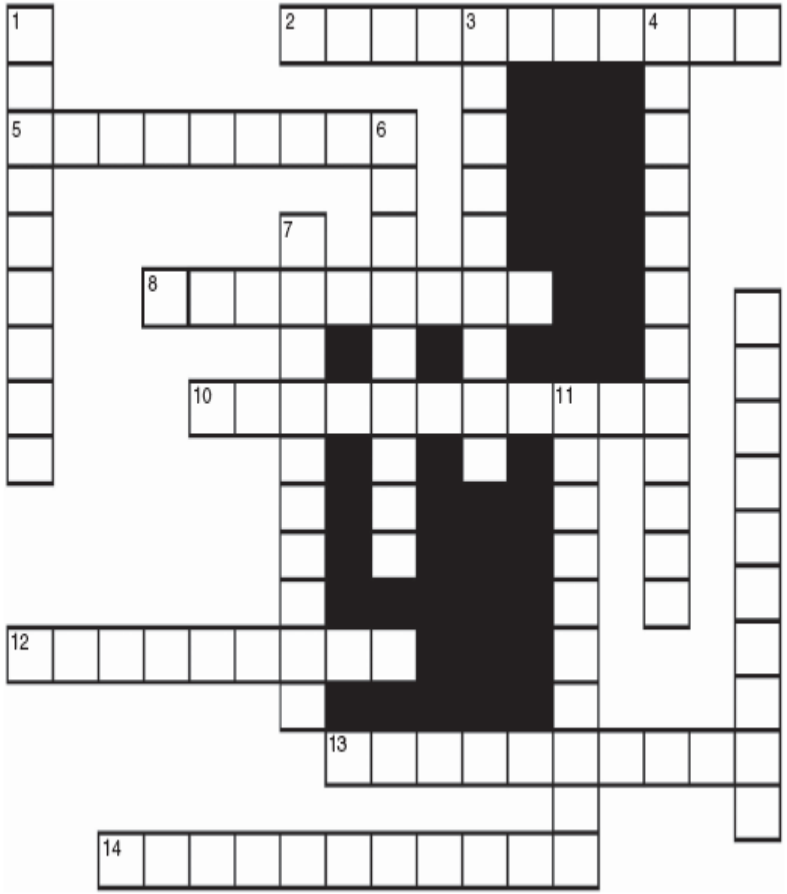
Tabla 2. Recomendación de ajuste de dosis de daptomicina según la tasa de filtración glomerular estimada por diferentes fórmulas

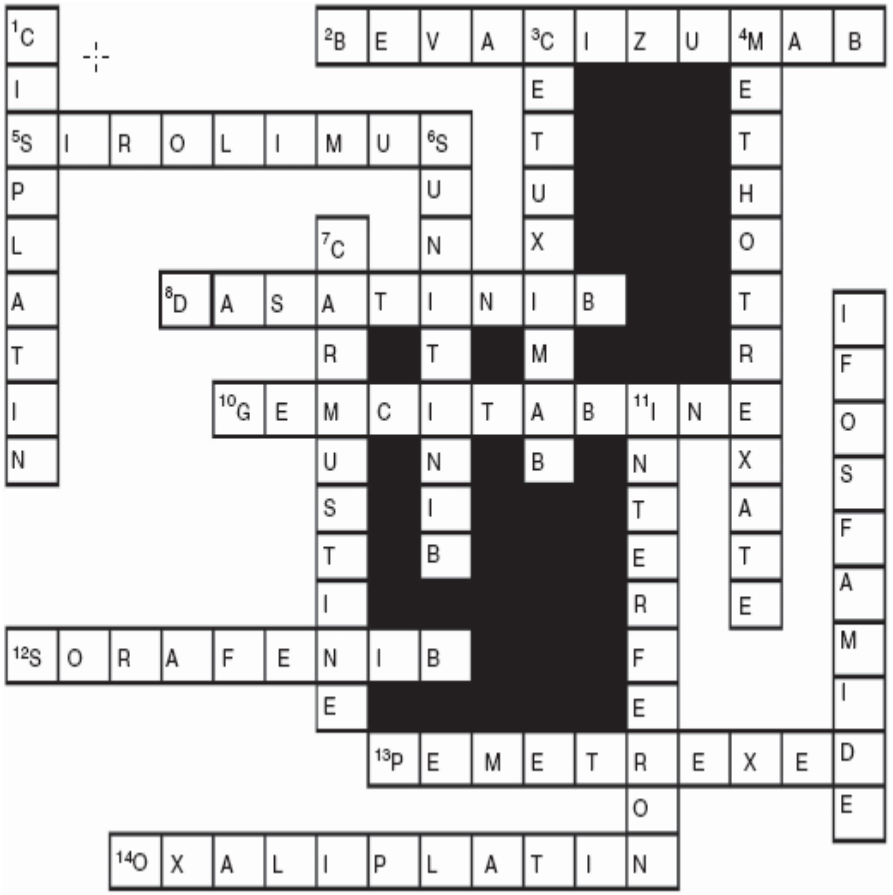
Fórmula utilizada para estimar la TFG	Resultado	Unidades	Recomendación según ficha técnica
Cockcroft-Gault	21,6	ml/min	/48 h
MDRD-4v	33	ml/min/1,73 m²	/24 h
MDRD-4v corregido por superficie corporal	27,5	ml/min	/48 h
CKD-EPI	31,5	ml/min/1,73 m²	/24 h

Mujer de 85 años de raza blanca, 150 cm de altura y 50 kg de peso, con creatinina en suero de 1,5 mg/dl. Superficie corporal estimada de 1,4 m².
TFG: tasa de filtración glomerular.

FÁRMACOS ANTINEOPLÁSICOS EN LA INSUFICIENCIA RENAL

AGENTES QUIMIOTERÁPICOS Y NEFROTOXICIDAD. ONCONEFROLOGÍA





ANTINEOPLÁSICOS - INSUFICIENCIA RENAL

- Los riñones son una importante vía de eliminación (filtración glomerular/ secreción tubular) de muchos antineoplásicos y de sus metabolitos
- Algunos detalles de su eliminación y metabolismo no son bien conocidos
- La IR puede afectar al metabolismo de algunos fármacos
- Ajustar dosis para disminuir toxicidad en la IRC y en HD
- Asociaciones fármacos:
  - Otros antineoplásicos
  - ATB. AINES. Antieméticos…..

FACTORES DE RIESGO-NEFROTOXICIDAD

- **Relacionados con el paciente**
  - Edad
  - Insuficiencia renal de base
  - Alteración de la respuesta inmune
    - Genes que la regulan y aumenten las reacciones alérgicas a los fármacos
  - Farmacogenética
    - Mutaciones hepáticas o renales de los sistemas enzimáticos (CYP450)
    - Trasportadores de proteínas. Trasportadores renales

- **Relacionados directamente con el riñón**
  - Tumores que afectan directamente (MM. Linfomas-leucemias)
  - Indirectamente:
    - Depleción volumen: vómitos, diarreas, poliuria
    - Depleción VC eficaz (IC. IH. Derrame pleural. Síndrome nefrótico).
    - Hipercalcemia. Hiperuricemia

- **Toxicidad del agente**
  - Nefrotóxicidad. Altas dosis. Asociación con ATB/AINES/Contrastes…
  - Metabolitos capaces de formar cristales en la luz tubular

- **Manejo renal de los fármacos**
  - Algunos de los sistemas enzimáticos renales favorecen la toxicidad de los fármacos mediante la formación de ROS, peroxidación lipídica, daños protéicos, alteración del los ácidos nucleicos…

¿COMO AJUSTAMOS LOS FÁRMACOS EN LA INSUFICIENCIA RENAL?

FICHA TÉCNICA DE LAS FÁRMACOS

- Poca información del método de estimación del FG
- Déficit de información sobre dosificación en insuficiencia renal
- Diferencias entre fichas técnicas del mismo producto
- No información, en general, sobre su uso en IR grave
- No información, en general, sobre su uso en pacientes en HD

NECESITAMOS OTRAS FUENTES DE INFORMACIÓN.
SERIES PEQUEÑAS. INFORMACIÓN "DISPAR"

CISPLATINO

Posología: pautas diferentes en función del tipo de neoplasia. Efectos secundarios: Nefrotóxico. Neurotóxico. Ototóxico. Hematológicos. Gastrointestinales

Con disfunción renal o depresión de la médula ósea, la dosis debe reducirse adecuadamente (Ferrer®).

No debe administrarse un ciclo repetido de cisplatino hasta que los niveles de creatinina sérica estén por debajo de 1.5 mg/dl o la urea sanguínea < 25 mg/dl.

Cisplatino está contraindicado en pacientes con:

Insuficiencia renal preexistente (Accord®) (Actavis®)

Con disfunción renal (Ferrer®)

Con disfunción renal (depuración de creatinina < 60 ml/min) (Strides®)

Insuficiencia renal grave (aclaramiento de creatinina inferior a 70 (µmol/l) (Pharmacia. Grupo Pfizer®)

CISPLATINO

La nefrotoxicidad (NTA. Microangiopatía trombótica. Magnesuria. Nefropatía pierde sal. DI nefrogénica. Fanconi) es dosis-dependiente y acumulativa. Hidratar adecuadamente.

Drug	Pharmacokinetics	Available Information	Recommendation
Cisplatin	Non-enzymatically transformed into multiple metabolites. There is good uptake of cisplatin in the kidneys, liver and intestine. Distributes into third spaces such as ascites and pleural fluid. The elimination of intact drug and metabolites is via the urine. In the first 24hrs 20-80% is excreted.	SPC (Pharmacia 2008) – Cisplatin induces nephrotoxicity, which is cumulative. It is therefore contra-indicated in patients with renal impairment. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.75 fraction of dose, for CrCl of 45ml/min, use 0.5 fraction of dose, for CrCl of 30ml/min cisplatin is contra-indicated. **BC Cancer Agency** –GFR>60mls/min ; 100%, GFR 45-59mls/min; 75% dose, <45mls/min ; hold cisplatin- delay with hydration/switch to carboplatin. **Bennett et al**[7] – GFR >50mls/min 100% dose; GFR 10-50mls/min 75% dose GFR <10mls/min 50% dose **Dialysis** **Haemodialysis** – Dialysed. Give 50% dose[7] NB. There is experience of using the same dose as the GFR. It should be noted, however, that there is no evidence for this practice. **BC Cancer Agency** -Advises dialysis within 3 hours of giving dose.	**GFR (ml/min)** — **Dose** >60 — 100% 45-59 — 75% <45 — consider carboplatin Consider carboplatin if GFR <45ml/min Conflicting information. Where GFR is less than 45mls/min - clinical decision. **Dialysis** – give 50% dose. Dialysis should be performed within 3 hours after giving dose.

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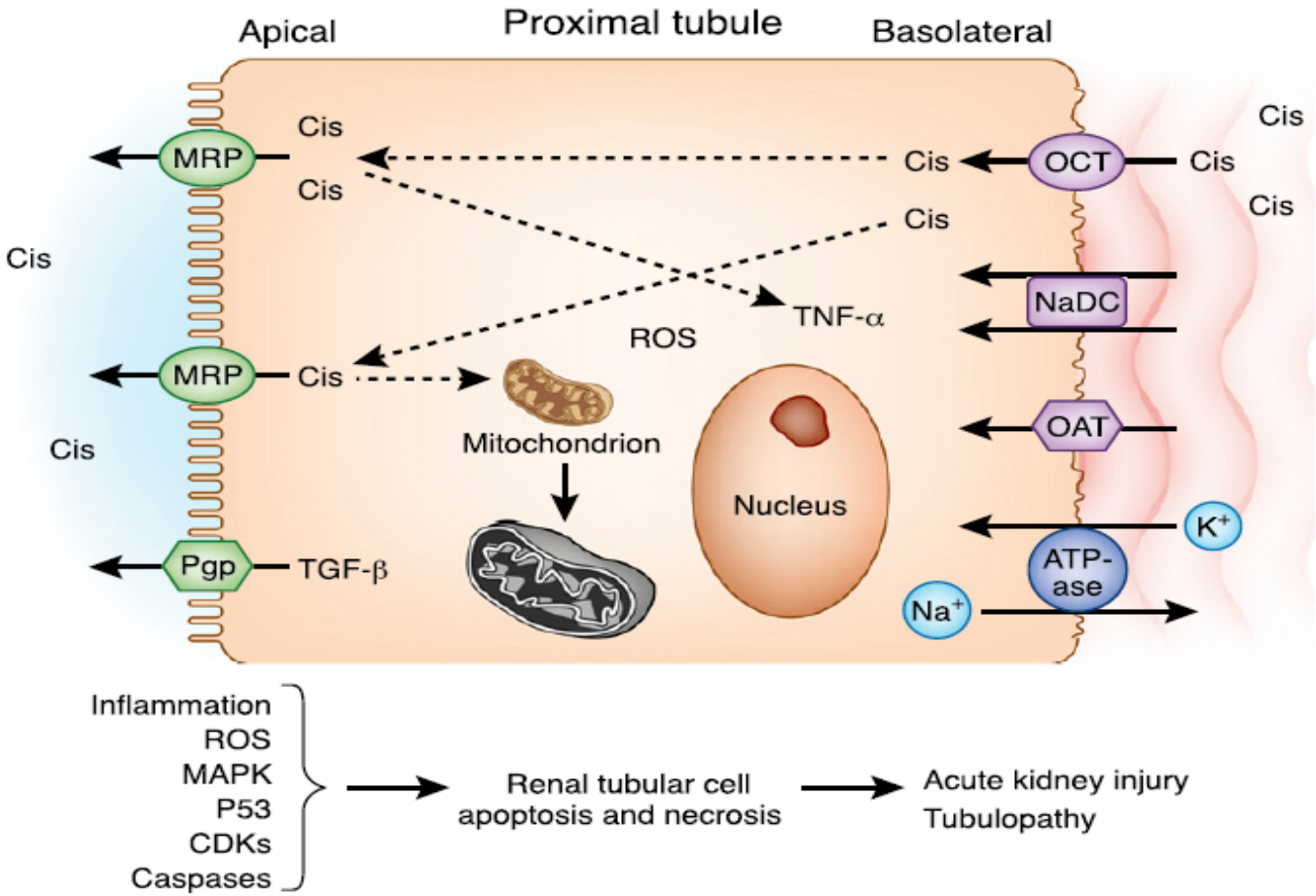
CISPLATINO


Apical
Proximal tubule
Basolateral
MRP
MRP
Pgp
Cis
Cis
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Cis
Cis
Cis
TNF-α
ROS
TGF-β
Mitochondrion
Nucleus
OCT
NaDC
OAT
K+
ATP-ase
Na+
Inflammation
ROS
MAPK
P53
CDKs
Caspases
Renal tubular cell apoptosis and necrosis
Acute kidney injury
Tubulopathy

CARBOPLATINO

Menos nefrotóxico que el cisplatino. Hipomagnesemia. NTA. Nefropatía pierde sal

Drug	Pharmacokinetics	Available Information	Recommendation
Carboplatin	There is little, if any, true metabolism of carboplatin. Excretion is primarily by glomerular filtration in urine, with most of the drug excreted in the first 6hrs. ~32% dose is excreted unchanged. Terminal t½ ~ 6 days.	**SPC (Hospira 2006)** – Dose reduce with renal impairment and monitor haematological nadirs and renal function. Myelosuppression is closely related to renal clearance. Carboplatin is contra-indicated with CrCl <20ml/min. **Faulding** – CrCl >40ml/min, max dose = 400mg/m^2 CrCl 20-39ml/min, max dose = 250mg/m^2 **Dialysis** **BC Cancer Agency** – In dialysis dependant chronic renal failure give a fixed dose of 100mg, if the patient has had previous platinum treatment, or 150mg if not. Dialysis should be performed 24 hours after the dose. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD - Dose as in normal renal function.	Dose using Calvert equation: Dose = AUC(25 + GFR) CI if CrCl <20ml/min Ccr: 40-60 (250 mg/m^2) Ccr: 15-40 (200 mg/m^2)

GFR: Cockroft / Wright. Peso ideal = ((peso actual – peso ideal) x 0.40) + peso ideal)

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DOCETAXEL

Ambos tienen Metabolismo hepático. Mínima excreción renal. No nefrotoxicidad

Drug	Pharmacokinetics	Available Information	Recommendation
Docetaxel	Cytochrome P-450 mediated metabolism. In animal studies distributed to all tissues and organs except the brain. 6% and 75% of the dose is excreted via the renal and faecal route respectively within 7 days. Terminal t½ = 2.5 hours.	**SPC (Sanofi Aventis 2008)** – No information **Aventis** – No dose adjustment necessary. 1 major and 3 minor metabolites have been identified and these are excreted in the faeces. **Dialysis** **Mencoboni et al, 2006** reported a case where the pharmacokinetics of docetaxel, pre and post-dialysis administration in a haemodialised patient were investigated. The results showed no apparent differences in the plasma concentration-time curves of docetaxel administered before or after dialysis. The authors concluded that docetaxel can be used in dialysis patients, with no dosage reduction needed, with docetaxel not being removed from the blood during dialysis[14]. **Renal Drug Handbook**- CAPD, HD, HDF/High flux. CAV/VVHD - unlikely dialysability – dose as in normal renal function.	No dose reduction necessary. **Dialysis** Dose as in normal renal function.

PACLITAXEL

Paclitaxel	Hepatic metabolism and biliary clearance is the principal mechanism for disposition. Mean values for cumulative urinary recovery of unchanged drug ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance.	**SPC (Abraxis Bioscience 2009)** – No recommendations **BMS** – within 24-48 hrs following administration, <10% of the dose appears in the urine. In dialysis patients, full dose has been given (on non-dialysis days) with a typical toxicity profile. **Dialysis** [26] - Paclitaxel chemotherapy is efficacious and feasible for patients undergoing haemodialysis (NB study was carried out in ovarian cancer at 150mg/m^2). **Bekele et al 2001**- reports a case of a patient that receives paclitaxel whilst on haemodialysis. The authors recommended dose reduction (135mg/m2) in dialysis patients [27]. **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function **BC Cancer Agency** – No adjustment necessary	No dose reductions necessary. **Dialysis** – clinical decision

GEMCITABINA

Nefrotoxicidad: microangiopatía trombótica

Drug	Pharmacokinetics	Available Information	Recommendation
Gemcitabine	Rapid metabolism by cytidine deaminase in the liver, kidney, blood and other tissues. The active intracellular metabolites have not been detected in plasma or urine. Urinary excretion of parent drug and inactive metabolite (dFdU) accounts for 99%. Terminal t½ is ~1 hour – this increases if the drug is administered over a longer period.	**SPC (Eli Lilly 2007)** – Use with caution in patients with impaired renal function. **Lilly** – Since gemcitabine is extensively metabolised by various tissues, mild to moderate renal insufficiency would not be expected to significantly affect its clearance, although there is a possibility of accumulation of the inactive metabolite, dFdU. Lilly investigated the Pharmacokinetics in 18 patients with renal insufficiency and found that there was no significant difference between patients on the basis of their GFR (GFR ranged from 30ml/min upwards). **Dialysis** Conventional intermittent haemodialysis should be performed before a weekly dose and again some 48 hours later. Provided this is carried out the patient should not face excess toxicity. **Renal Drug Handbook** – Likely to be dialysed by CAPD, HD, CAV/VVHD, HDF/High Flux.	CrCl>30ml/min – standard dosing CrCl<30ml/min – consider dose reduction – clinical decision. **Dialysis** Likely to be dialysed but no information on dosing.

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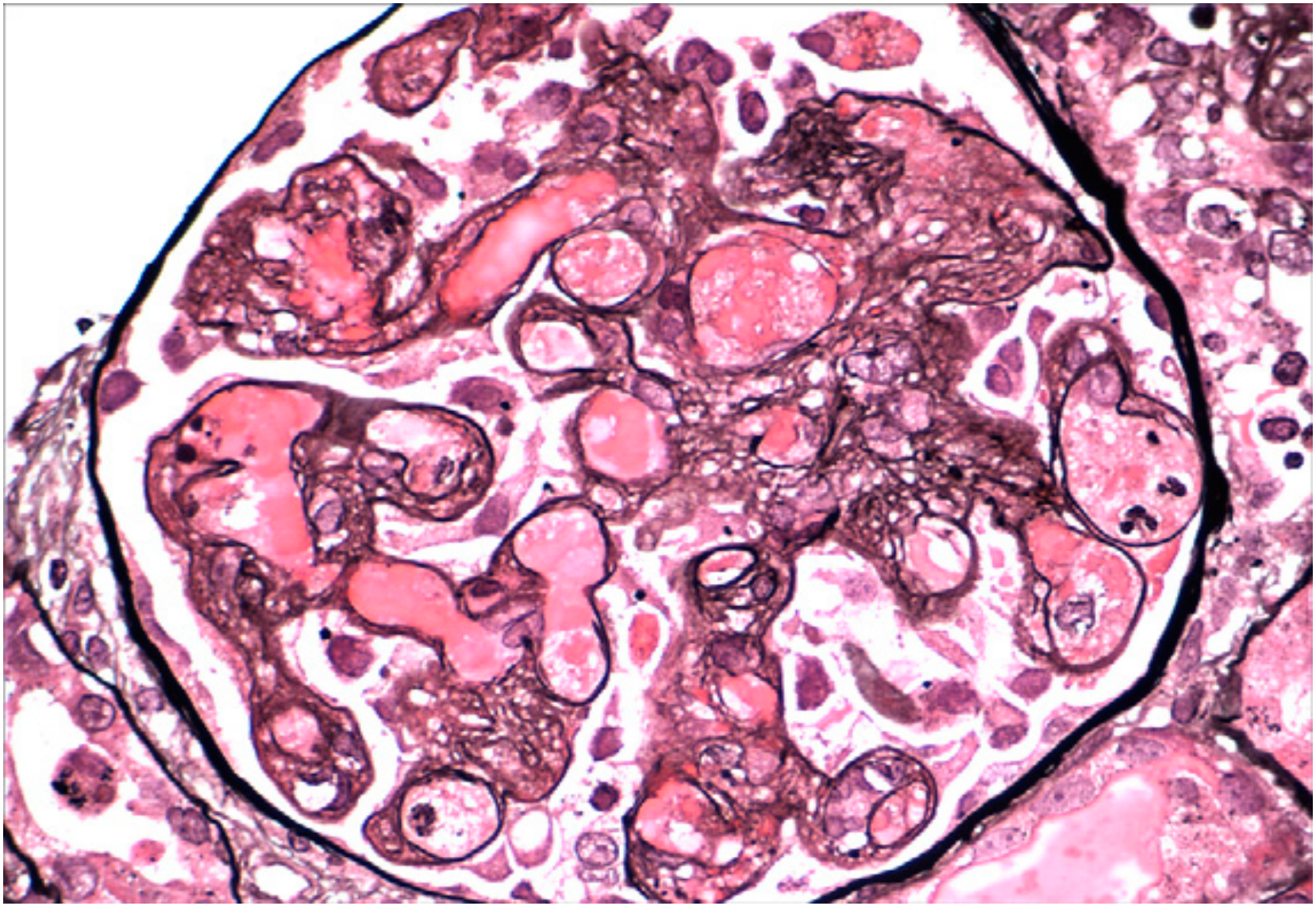

PEMETREXED

Nefrotoxicidad: NTA. Diabetes Insípida nefrogénica. Fanconi. Acidosis tubular.

Drug	Pharmacokinetics	Available Information	Recommendation
Pemetrexed	Not metabolised to an appreciable extent. Mainly excreted (70-90%) unchanged in the urine.	**SPC (Eli Lilly 2009)** – Drug can be safely given if GFR>45mls/min, lower than this adjustments cannot be recommended. **Lilly** – Case report of a patient receiving grade 3-4 toxicity after administration with a GFR 19mls/min. **BC Cancer Agency** - GFR<45 delay treatment	GFR>45mls/min 100% dose Otherwise clinical decision May be hazardous in severe renal impairment.

No información HD

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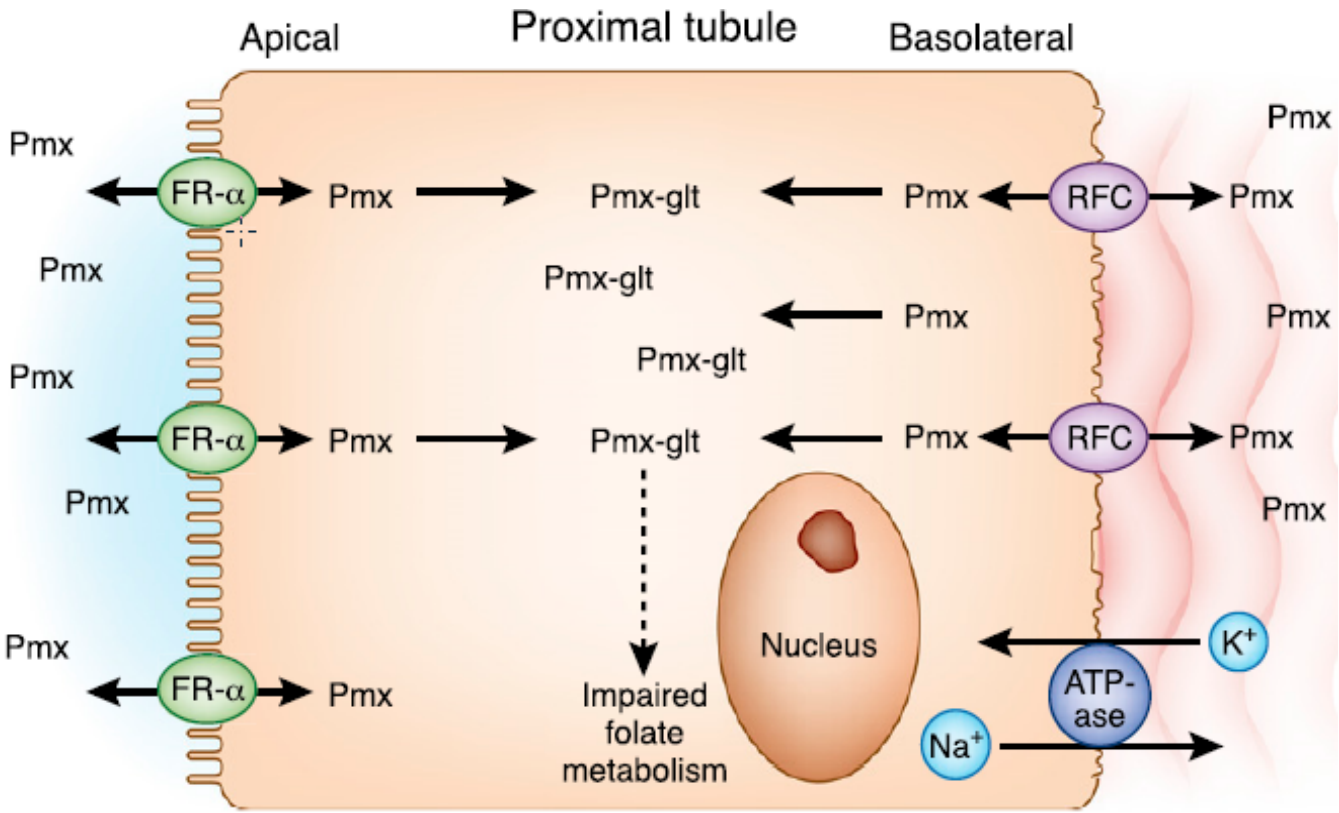
PEMETREXED


Apical
Proximal tubule
Basolateral
Pmx
FR-α
Pmx
Pmx-glt
Pmx
RFC
Pmx
Pmx
Pmx-glt
Pmx
Pmx
Pmx-glt
Pmx
FR-α
Pmx
Pmx-glt
Pmx
RFC
Pmx
Pmx
Pmx
Nucleus
K+
Pmx
FR-α
Pmx
Impaired
folate
metabolism
ATP-
ase
Na+
Polyglutamylated-
pemetrexed
Inhibits enzymes
and impairs
RNA/DNA synthesis
Acute kidney injury
Tubulopathy

ETOPOSIDO

Nefrotoxicidad: Síndrome lisis tumoral

Drug	Pharmacokinetics	Available Information	Recommendation
Etoposide	Liver metabolised, yielding inactive metabolites. ~45% of an administered dose is excreted in the urine, 29% being excreted unchanged in 72 hrs. Up to 16% recovered in the faeces.	**SPC (medac GmbH 2007)** – If GFR - >50ml/min ; 100% dose, 15-50mls/min; 75% dose, no specific information for GFR< 15ml/min however further dose reduction should be considered. Subsequent etoposide dosing should be based on patient tolerance and clinical effect. **BMS** – Creatinine clearance is the strongest predictor of etoposide clearance. US prescribing information suggest a 25% dose reduction for GFR between 15–50 ml/min[16]. Subsequent dosing should be based on patient tolerance and clinical effect. A further dose reduction should be considered with GFR<15ml/min. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.85 fraction of dose, for CrCl of 45ml/min, use 0.8 fraction of dose, for CrCl of 30ml/min, use 0.75 fraction of dose. **Textbook of drug prescribing in renal failure and BC Cancer Agency** – GFR 10-50ml/min; 75% dose. Below 10 = 50% of dose. **Dialysis** **Holthius et al**[17] reported comparable pharmacokinetics in patients receiving haemodialysis for doses of etoposide up to 127mg/m^2 in relation to patients with normal renal function. **Sauer et al**[9] and **Brindley et al**[18] found that etoposide is not removed by dialysis. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD – 50% dose then base on clinical response.	**CrCl (ml/min)** – **Dose** >50 – 100% 15-50 – 75% <15 – 50% Subsequent doses should be based on clinical response. **Dialysis** Start at reduced dose and increase according to clinical response.

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VINORELBINA

Nefrotoxicidad: hiponatremia

Drug	Pharmacokinetics	Available Information	Recommendation
Vinorelbine	Widely distributed in the body, mostly in spleen, liver, kidneys, lungs, thymus; moderately in heart, muscles; minimally in fat, brain, bone marrow. High levels found in both normal and malignant lung tissues, with slow diffusion out of tumour tissue. Metabolism appears to be hepatic. t½ is greater than 40hrs. Excretion is mainly by the biliary route (18.5% appears in the urine)	**SPC (Medac GmbH 2007)** – There is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function. **Pierre-Fabre** – Clearance is mainly hepatic. **Renal Drug Handbook** – No dose reduction. **BC Cancer Agency** – No dose adjustments necessary. **Dialysis** **BC Cancer Agency** - Reduction from 25 mg/m² to 12.5 mg/m² IV for one dose on day 1 weekly (given after hemodialysis) was reported in one patient. **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function and monitor closely.	No dose reduction necessary

University College London Hospital - Dosage Adjustment for Cytotoxics in Renal Impairment (January2009)

TOPOTECAN

No asociado con nefrotoxicidad

Drug	Pharmacokinetics	Available Information	Recommendation
Topotecan	Undergoes reversible, pH-dependent hydrolysis of the active lactone moiety to the inactive hydroxyacid (carboxylate) form. A relatively small amount of topotecan is metabolised by hepatic microsomal enzymes to an active metabolite, *N*-demethyltopotecan. The clinical significance of this metabolite is not known. Excretion via biliary and renal route. 20-60% is excreted in the urine as topotecan or the open ring form.	**SPC (GSK 2009)** – There is no experience of the use of topotecan in patients with CrCl < 20 ml/min and topotecan is contra-indicated in this group of patients. Plasma clearance in patients with CrCl 41-60ml/min is decreased to ~67%. In moderate renal impairment, plasma clearance was reduced to ~34%. **Merck** – Dose-limiting toxicities, mainly neutropenia and thrombocytopenia are seen in patients with impaired renal function. In patients with moderate renal impairment, a starting dose of 0.75mg/m^2 is recommended. Further reductions are recommended in heavily pre-treated patients. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.8 fraction of dose, for CrCl of 45ml/min, use 0.75 fraction of dose, for CrCl of 30ml/min, use 0.7 fraction of dose. **BC Cancer Agency**-GFR 40-60ml/min =100% dose, 20-39= 50%, < 20 =not recommended. **Dialysis** Topotecan is effectively cleared by HD. Plasma clearance may be increased fourfold whilst on HD[28]. **Renal Drug Handbook** – CAV/VVHD – 0.5-0.75mg/m^2/day and monitor closely.	**CrCl (ml/min)** — **Dose** >40 — 100% 20-39 — 50% <20 — CI

University College London Hospital - Dosage Adjustment for Cytotoxics in Renal Impairment (January2009)

BEVACIZUMAB

No se ha estudiado la seguridad y eficacia en pacientes con IR.

Se recomienda continuar el tratamiento hasta la progresión de la enfermedad subyacente o hasta toxicidad inaceptable.

Nefrotoxicidad: HTA y Proteinuria (Interrumpir Sd. Nefrótico).
NTIA. Microangiopatía trombótica.

INHIBIDORES DE LA TIROSIN QUINASA

- **ERLOTINIB**
  - **No se recomienda su uso en IR grave**
- **GEFITINIB**
  - **En pacientes con Ccr ≤ 20 ml/min los datos son limitados, se recomienda su uso con precaución.**
- **AFATINIB**
  - **No se recomienda su uso en IR grave**
- **CRIZOTINIB**
  - **No se recomienda su uso en IR grave**

RECOMENDACIONES AJUSTE DE CITOTÓXICOS EN HD

Drug	Primary elimination pathway	Metabolites	Dosage adjustment, yes/no	Timing of administration	Recommended dose in HD	Grading of the recommendation
5-FU	Respiratory	Active	No	After HD	Standard dose	C
Capecitabine	Urinary	Active	Yes	After HD[a]	No data[a]	–
Carboplatin	Urinary	No data	Yes	After HD	Dose = AUC × (25 + 0) [21]	B
Cisplatin	Urinary	Inactive[b]	Yes	After HD	Reduction of 50%–75%	B
Cyclophosphamide	Urinary	Active and inactive	Yes	After HD	Reduction of 25%	B
Docetaxel	Faeces	Inactive	Yes	After or before HD	65 mg/m^2	C
Doxorubicin	Faeces	Active and inactive	No	After HD	Standard dose	C
Epirubicin	Faeces	Active	No	After HD	Standard dose	C
Etoposide	Faeces	Active	Yes	After or before HD	Reduction of 50%	B
Gemcitabine	Urinary	Inactive	No	6–12 h before HD	Standard dose	B
Irinotecan	Faeces	Active and inactive	Yes	After HD	No data	–
Methotrexate	Urinary	Active and inactive	Yes	After HD[a]	Reduction of 75%[a]	C
Oxaliplatin	Urinary	Active and inactive	Yes	After HD[a]	Reduction of ~30%[a]	C
Paclitaxel	Faeces	Inactive	No	After or before HD	Standard dose	B
Vinorelbine	Faeces	Active	Yes	After HD	i.v.: Reduction of 20%–33%	C

N. Janus et all Annals of Oncology 21: 1395–1403, 2010

.....PERO.....

¿CÓMO CALCULAMOS LAS DOSIS CUANDO NO TENEMOS REFERENCIAS?

- **VIGILANCIA DE LOS EFECTOS SECUNDARIOS**
  - **Hematológicos**
  - **Hepáticos**
  - **Renales**
  - **Digestivos**
  - **Neuropáticos**
  - **Otros**

- **REDUCCIÓN DOSIS**
- **PROLONGACIÓN DEL INTERVALO**
- **CAMBIO AGENTE**
- **SUSPENSIÓN**

CONCLUSIONES

- Muchos pacientes en el momento del diagnóstico presentan ERC
- Dificultad "real" para una dosificación ajustada de algunos fármacos en IR / HD
- La IR y la diálisis NO son una CONTRAINDICACIÓN para tratar
- Cruce de caminos entre oncología y nefrología que incluye:
  - Pruebas diagnósticas
  - Eventos agudos
  - Eventos crónicos
  - Nefrotoxicidad
  - *Dosificación fármacos*
- Necesidad de avanzar en el desarrollo de la ONCONEFROLOGÍA

GRACIAS