CORSO EDUCAZIONALE COMMISSIONE ANZIANI

XIII EDIZIONE

Giardini Naxos - Marriott Delta Hotels
17-18 aprile 2026

FONDAZIONE ITALIANA LINFOMI

Il punto di vista dell'onco-nefrologo nella gestione della tossicità renale

Prof. Mariadelina Simeoni
Università della Campania "Luigi Vanvitelli"

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

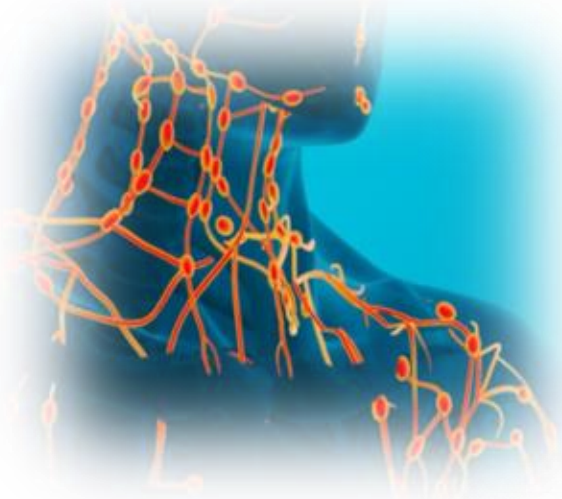
ONCO-ERA

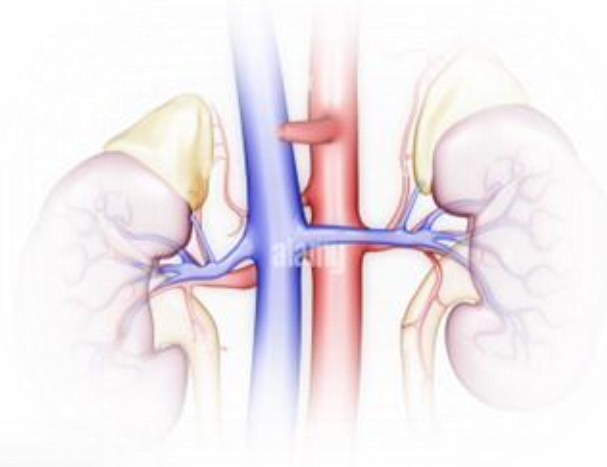
AOV: Azienda Ospedaliera Universitaria Luigi Vanvitelli

V: Università degli Studi della Campania Luigi Vanvitelli

biogem

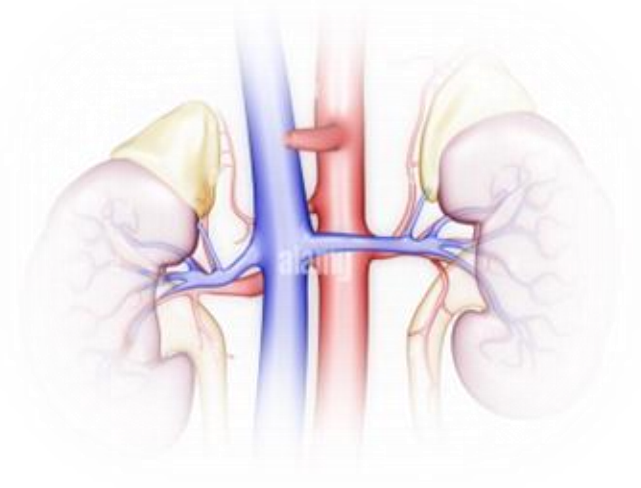
ERKNet per i pazienti



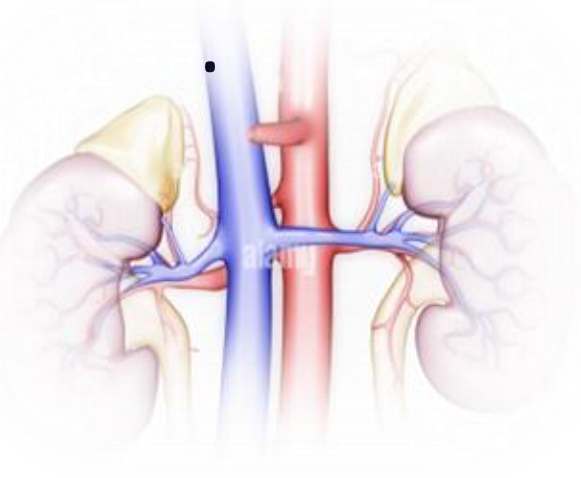


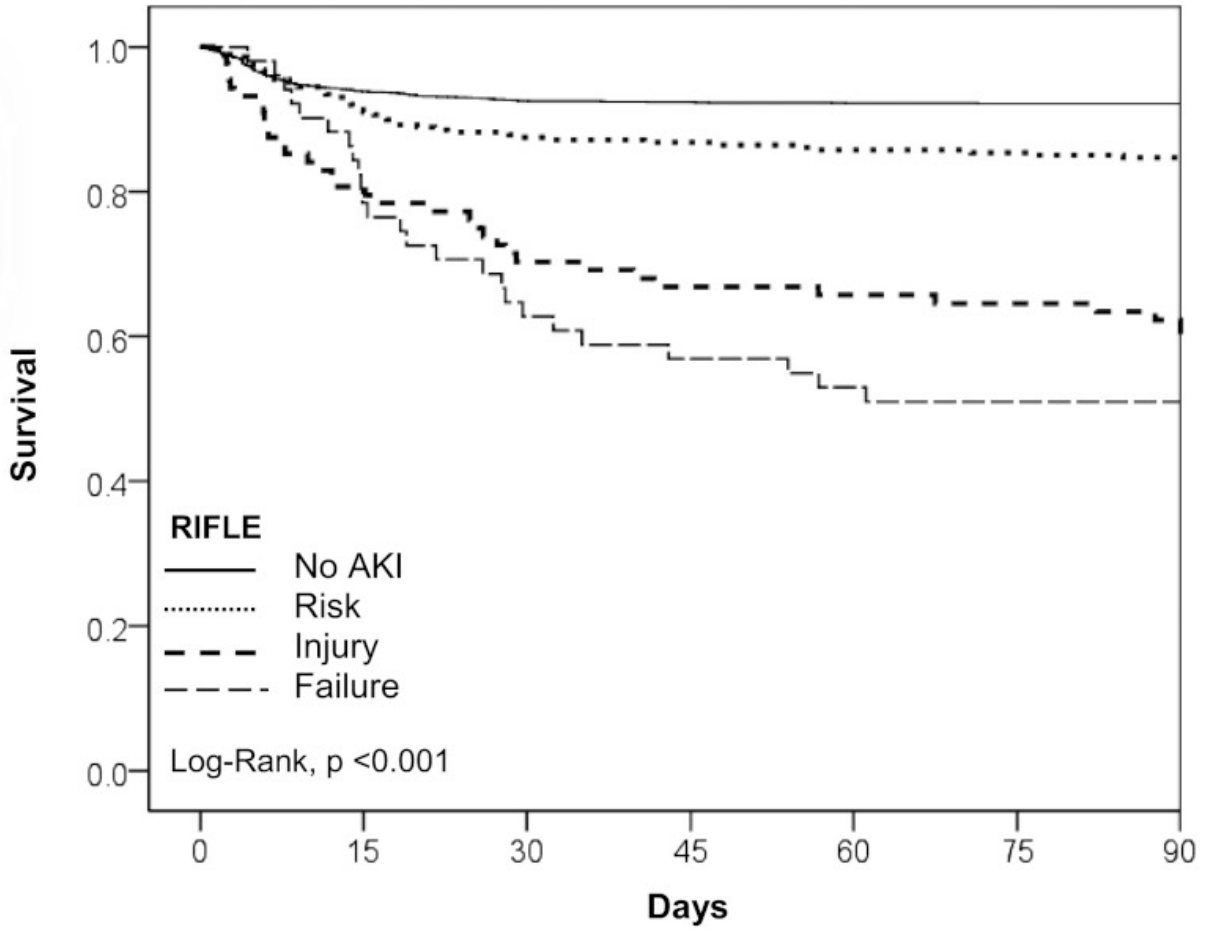
AKI incidence in old patients with lymphomas

- 17,5% - 27% of all age patients
- 34 - 46% of patients older than 75y



Renal complications reduce cancer patient survival

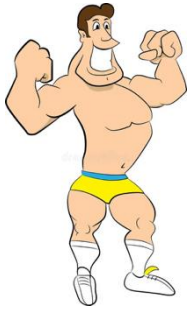


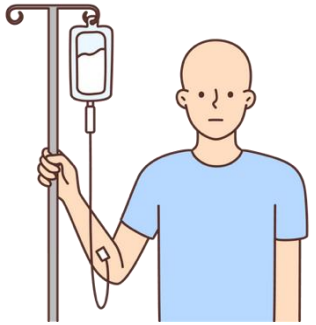


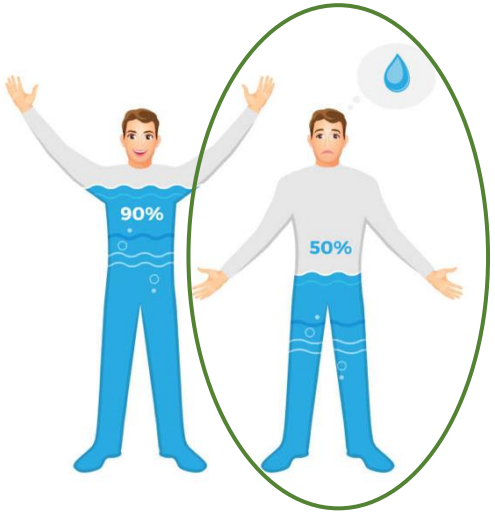
Number at risk							
No AKI	3131	2939	2898	2893	2888	2886	2886
Risk	288	263	253	251	248	247	245
Injury	88	71	62	59	58	57	55
Failure	51	40	32	29	27	26	26

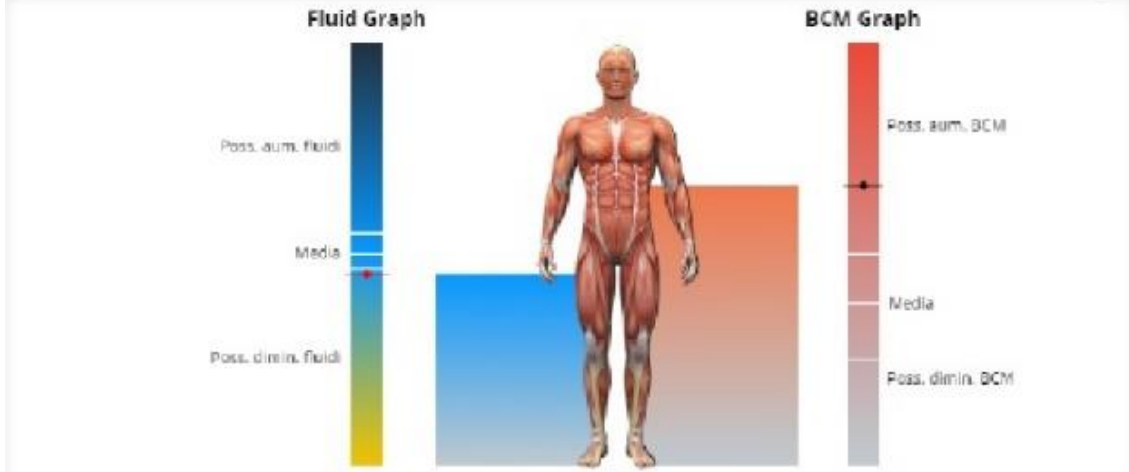
Salaudeen AK et al. C-JASN 2013

Distribution volume of drugs: it differs between individuals









	Risultato	U.d.m.	Percentuale	Intervallo di riferimento
Sesso	M			
Età	36			
Altezza	170	cm		
Peso corporeo	70	kg		
Resistenza (R)	440	Ω		
Reattanza (Xc)	70	Ω		
PA angolo di fase	9 °	gradi		[≥
BCM massa cellulare	35.1	kg	50.2 %	[≥
BCMm	22.4	kg		
BCM/h²	12.15	kg/m²		
BMR metabolismo basale	1987	kcal		
DEE disp. energetico giornaliero	3280	kcal		
SM massa muscolare	25.5	kg	36.4 %	
SMI	11.34	kg/m²		
FFM massa magra	58.1	kg	83.1 %	
FFM/h²	20.1	kg/m²		
FM massa grassa	11.9	kg	16.9 %	
FM/h²	4.1	kg/m²		
BMI indice di massa corporea	24.22	kg/m²		
ECM massa extra-cellulare	23	kg	32.9 %	
ECM/BCM	0.66			

Analisi dei fluidi

	Risultato	U.d.m.	Percentuale	Intervallo di riferimento
TBW acqua totale	41.9	L	59.9 %	[≥
ECW fluidi extra-cellulari	15.1	L	35.9 %	[
ICW fluidi intra-cellulari	26.9	L	64.1 %	[>
ECW/ICW	0.56			

ORIGINAL RESEARCH · Volume 9, Issue 8, 103666, August 2024 · *Open Access*

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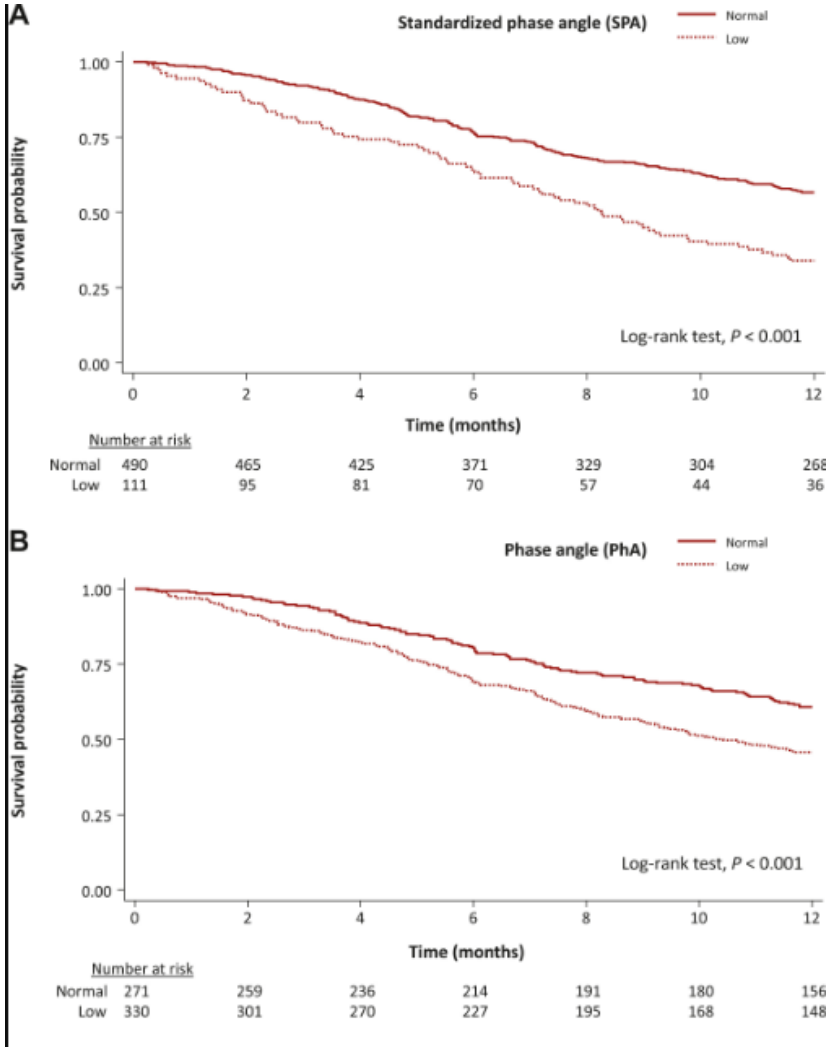
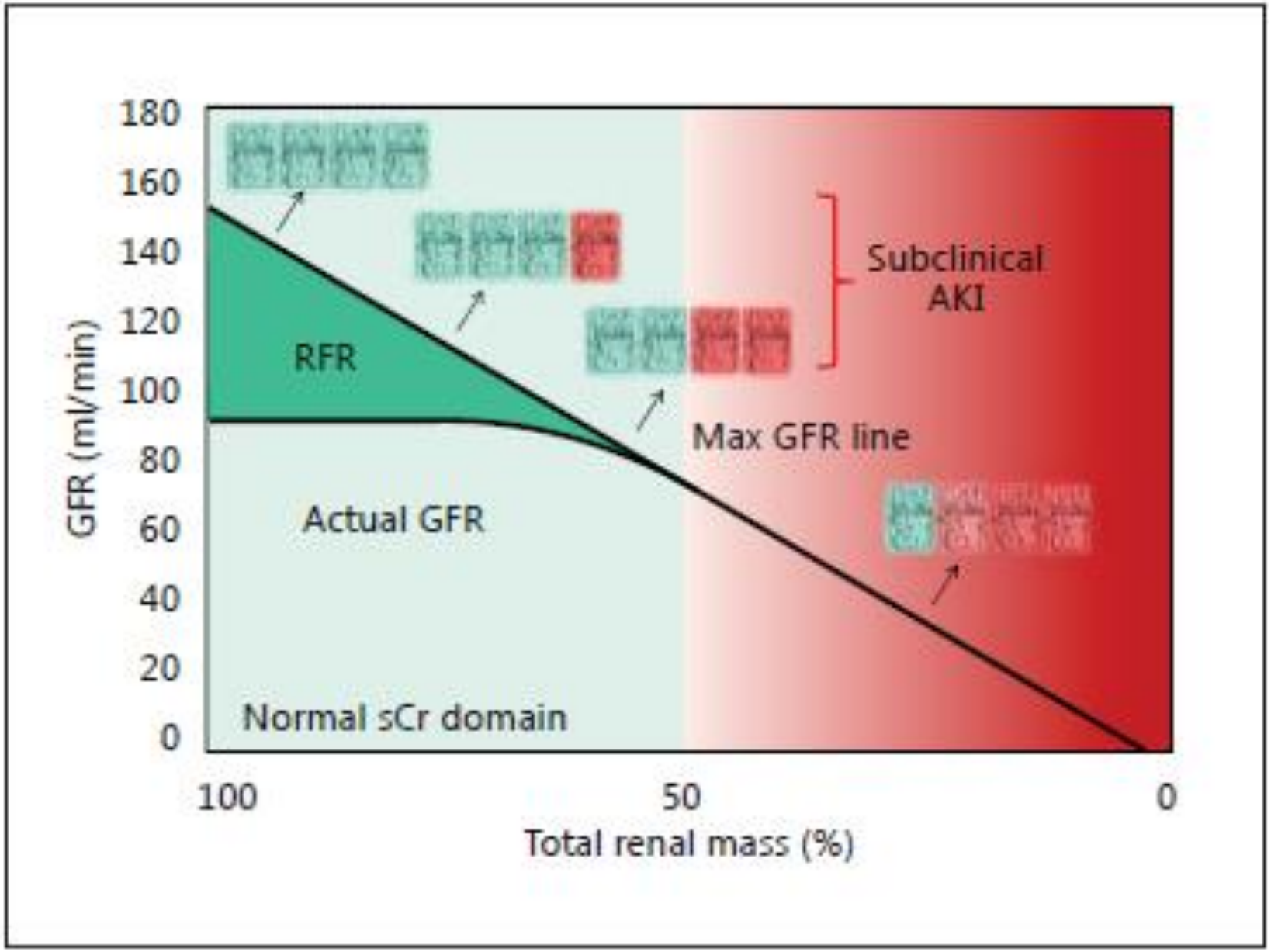
Bioimpedance-derived body composition parameters predict mortality and dose-limiting toxicity: the multicenter ONCO-BIVA study

E. Cereda [1] · A. Casirati [1] · C. Klersy [2] · ... · P. Pedrazzoli [6,7] · R. Caccialanza [1] on behalf of the ONCO-BIVA Collaborative Group [†] ...



640 pts with cancer
Receiving primary systemic treatment

Renal functional reserve during AKI can mask a large renal damage

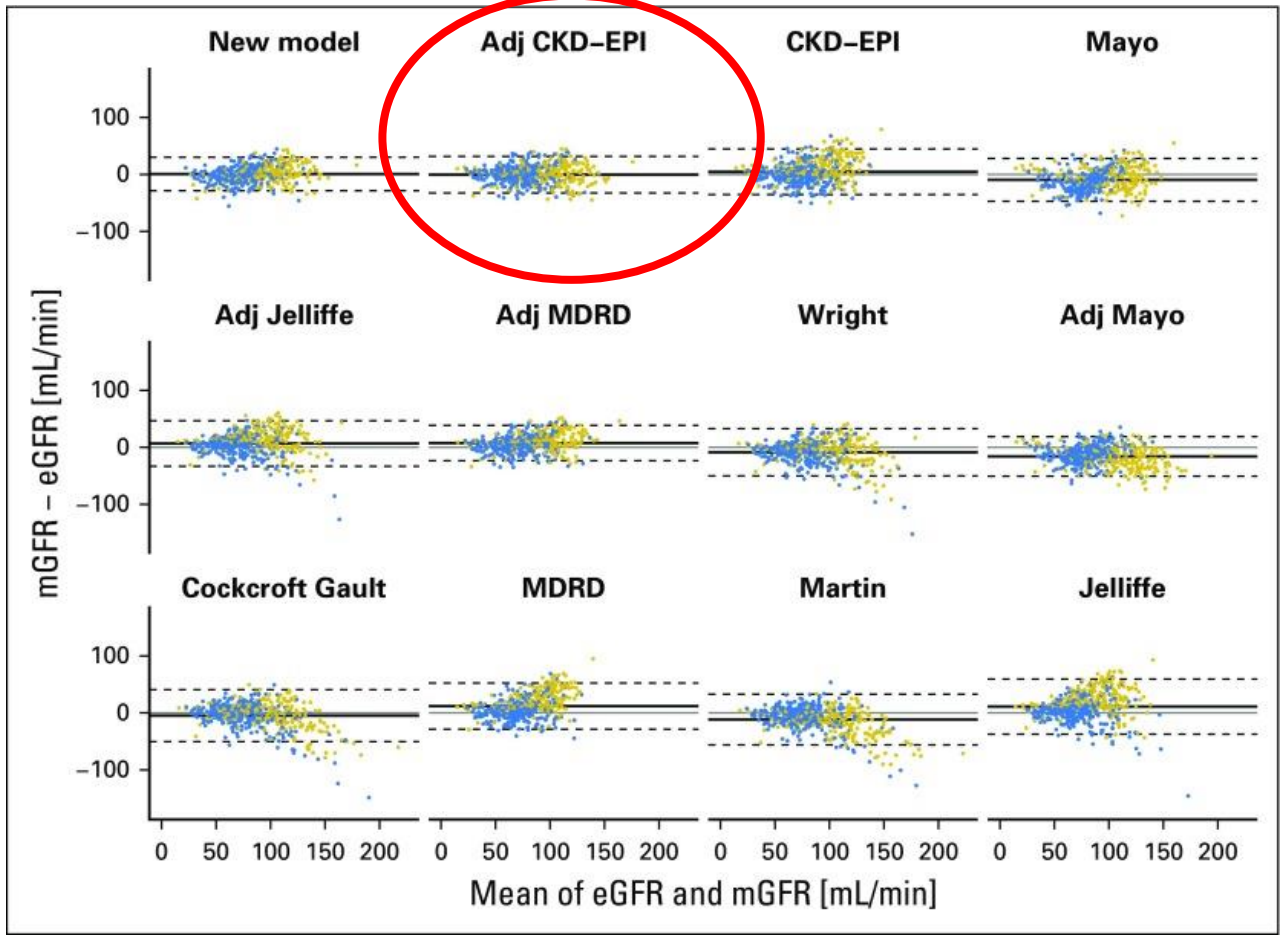


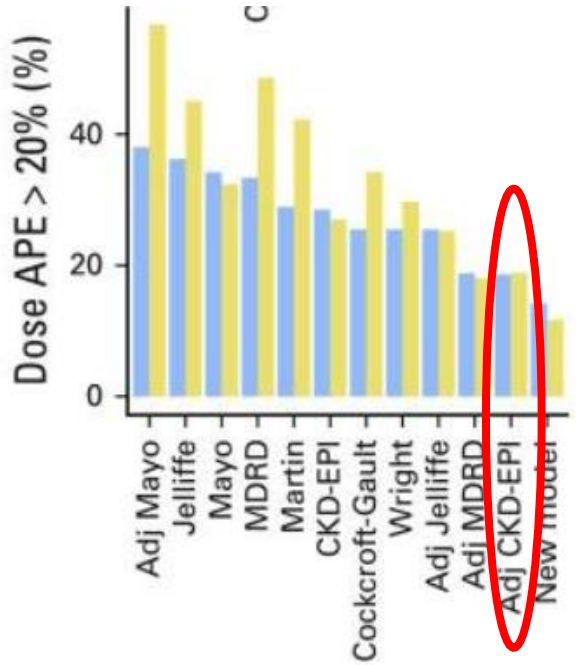
Sharma et al. Nephron Clin Pract 2014

How to measure or estimate the GFR in the cancer patient?

Janowitz et al (2017) J Clin Onc. : eGFR different models vs ^{51}Cr-EDTA clearance

N=2471



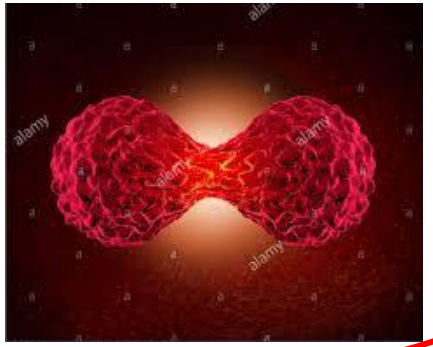


http://tavarelab.cruk.cam.ac.uk/JanowitzWilliamsGFR/

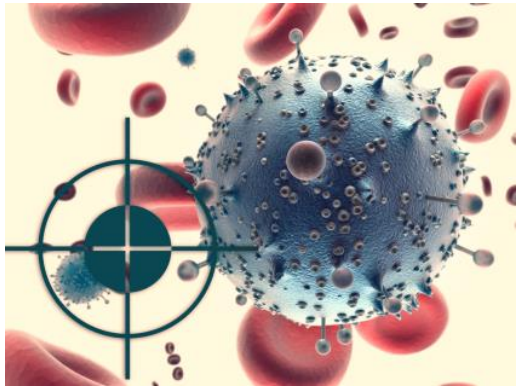
Janowitz et al : Am J Onc 2017

Drugs in Oncology:

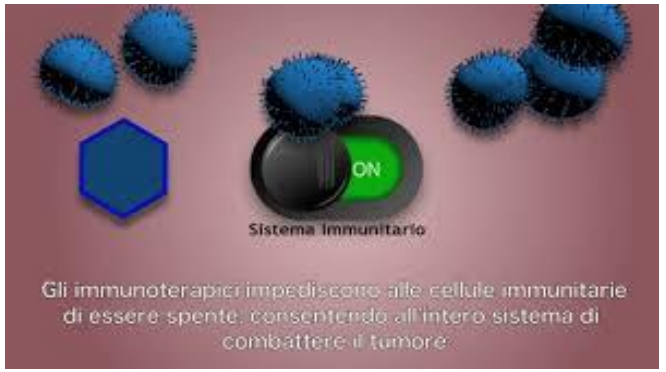
Cytotoxic Agents



Targeted Chemiotherapic Agents

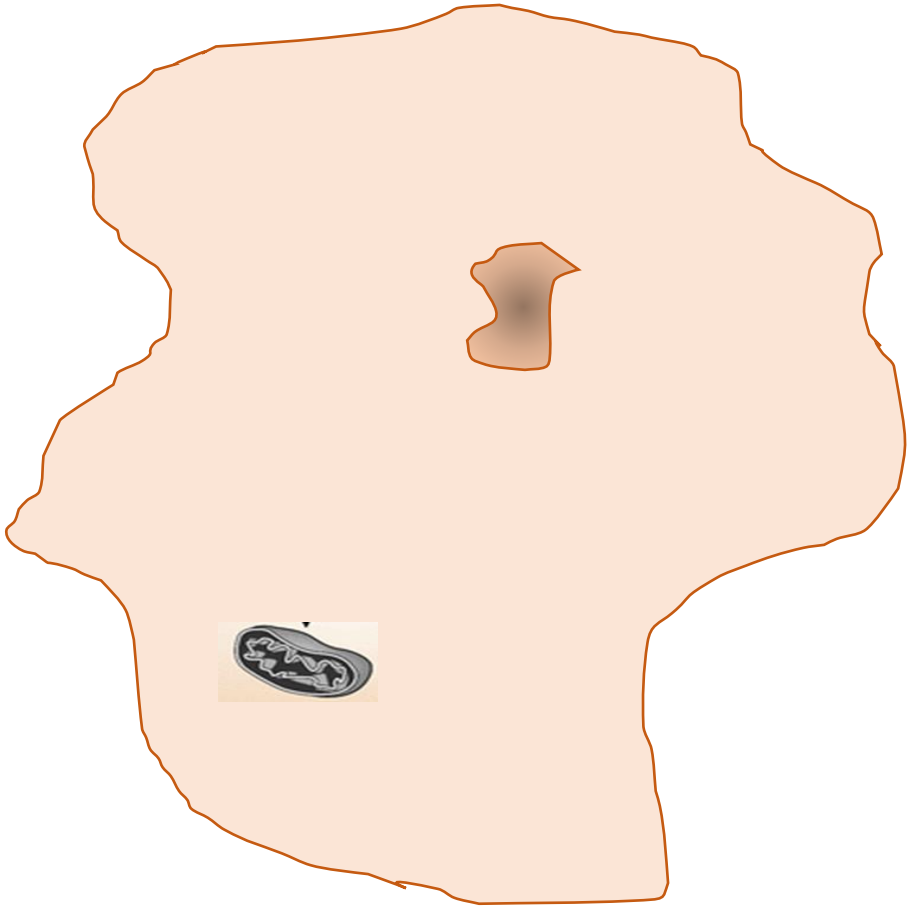


Immunotherapic Agents



Class of cytoxic drugs	Farmaci	Nefrotossicità
Alchilants	• Iphosphamide • Ciclofosphamide	Tubular toxicity: AKI, Fanconi
Platinum derived	• Cisplatin • **Oxaliplatin** • Carboplatin	Tubular toxicity: AKI, Fanconi
Antimetabolites	• Gemcitabine • Pemetrexed • **High dose Metotrexate** • 5 Fluorouracile • Capecitabine	Tubular toxicity due to precipitates AKI TMA
Anticancer antibiotics	• Mitomicine • Doxorubicine	Podocitopatia TMA
Anti-microtubular drugs	• Vincristine • Vinblastine • Paclitaxel	SIADH
Topo-isomerases inhibitors	• Etoposide • Irinotecan	Rare tubular damage

Platinum agents tubular handling: Oxaliplatin

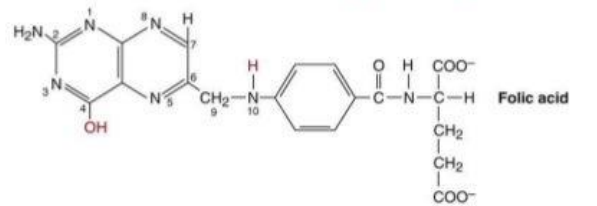


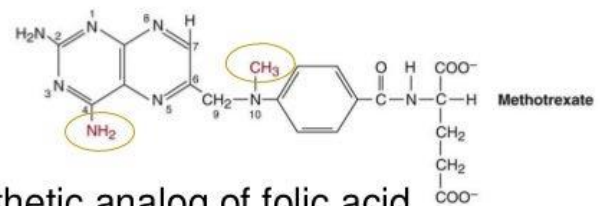
Ciarimboli et al. Am J Pathol 2010

Study or Subgroup	Mg Events	Mg Total	Non-Mg Events	Non-Mg Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 cisplatin <=50 mg/m2						
Ashrafi 2019	5	22	1	24	3.5%	6.76 [0.72, 63.33]
Minzi 2020	10	49	27	50	12.1%	0.22 [0.09, 0.53]
Yamamoto 2016	11	37	25	37	11.0%	0.20 [0.08, 0.54]
Yamamoto 2015	1	14	10	14	3.3%	0.03 [0.00, 0.32]
Subtotal (95% CI)		**122**		**125**	**29.9%**	**0.29 [0.07, 1.17]**
Total events	27		63			
Heterogeneity: $Tau^2 = 1.40$; $Chi^2 = 11.87$, df = 3 (P = 0.008); $I^2 = 75\%$						
Test for overall effect: Z = 1.75 (P = 0.08)						
2.1.2 50mg/m2< cisplatin<=60mg/m2						
Yamaguchi 2017	9	60	20	62	12.1%	0.37 [0.15, 0.90]
Matsui 2018	9	92	15	66	12.0%	0.37 [0.15, 0.90]
Yoshida 2014	23	161	133	335	17.6%	0.25 [0.15, 0.41]
Kidera 2014	4	67	123	334	10.4%	0.11 [0.04, 0.31]
Subtotal (95% CI)		**380**		**797**	**52.2%**	**0.26 [0.16, 0.41]**
Total events	45		291			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 4.07$, df = 3 (P = 0.25); $I^2 = 26\%$						
Test for overall effect: Z = 5.87 (P < 0.00001)						
2.1.3 60mg/m2<cisplatin<=80mg/m2						
Saito 2017	20	29	27	29	5.8%	0.16 [0.03, 0.85]
Kimura 2018	3	56	24	65	8.2%	0.10 [0.03, 0.34]
Oka 2014	1	44	9	41	3.9%	0.08 [0.01, 0.69]
Subtotal (95% CI)		**129**		**135**	**17.9%**	**0.11 [0.04, 0.27]**
Total events	24		60			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.34$, df = 2 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 4.76 (P < 0.00001)						
Total (95% CI)		**631**		**1057**	**100.0%**	**0.22 [0.14, 0.35]**
Total events	96		414			
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 18.89$, df = 10 (P = 0.04); $I^2 = 47\%$						
Test for overall effect: Z = 6.46 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 2.82$, df = 2 (P = 0.24), $I^2 = 29.2\%$						

J Li et al., Clin and Exp Nephr 3 Aug 2023

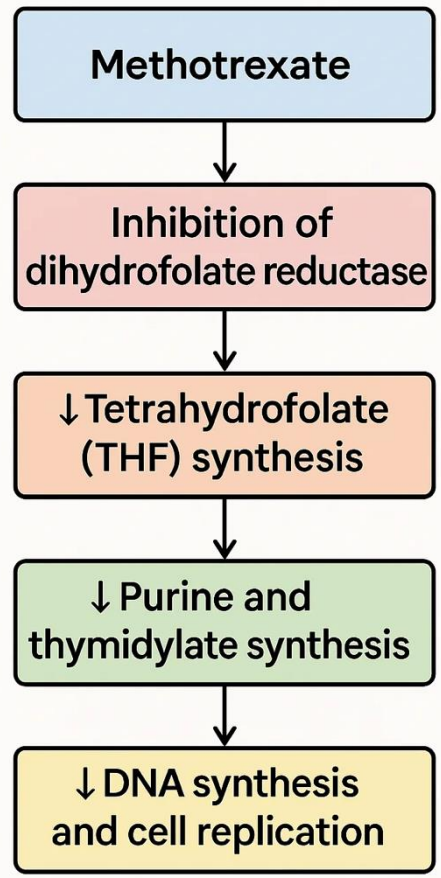
Antifolates: Methotrexate (MTX)

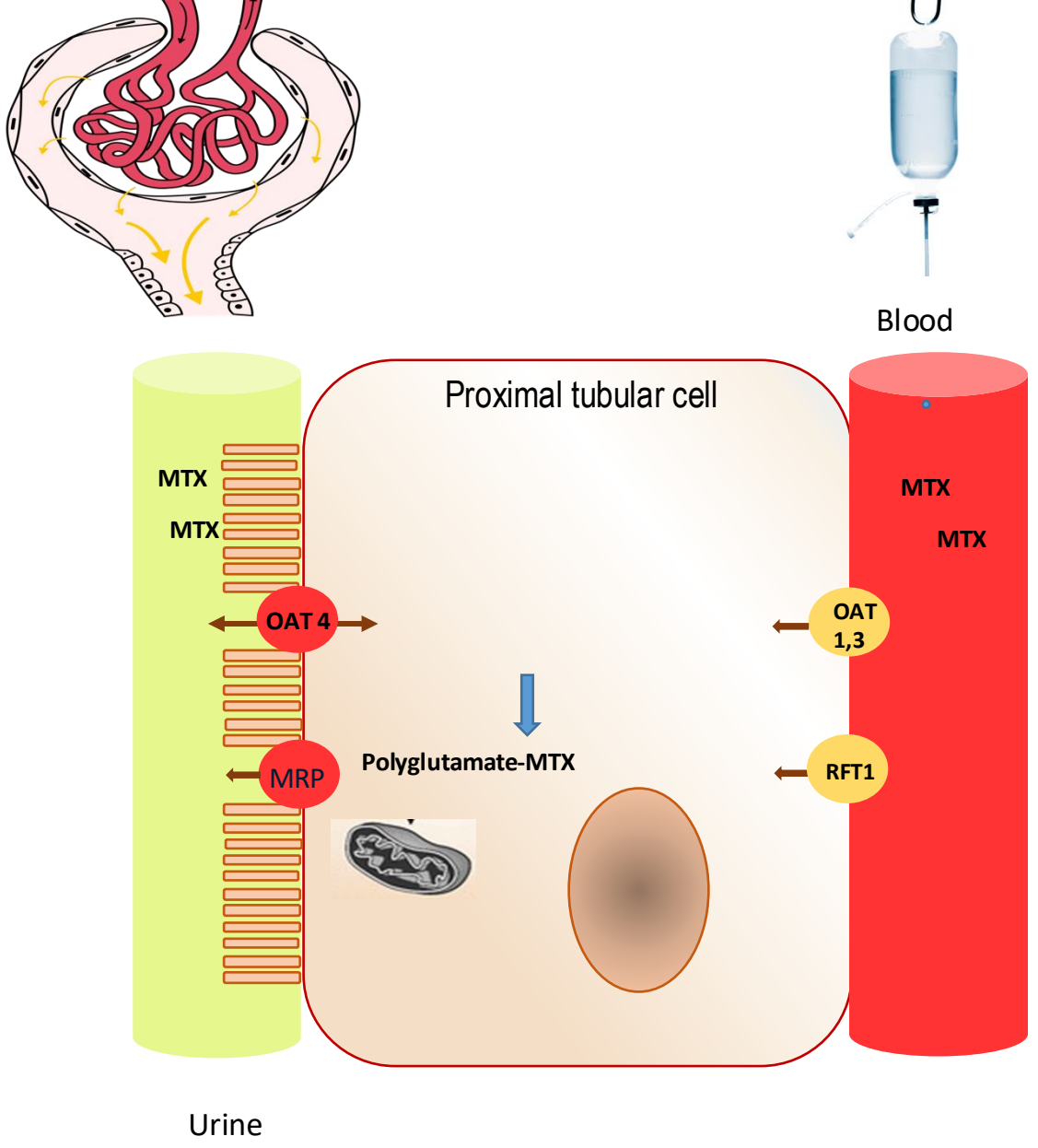




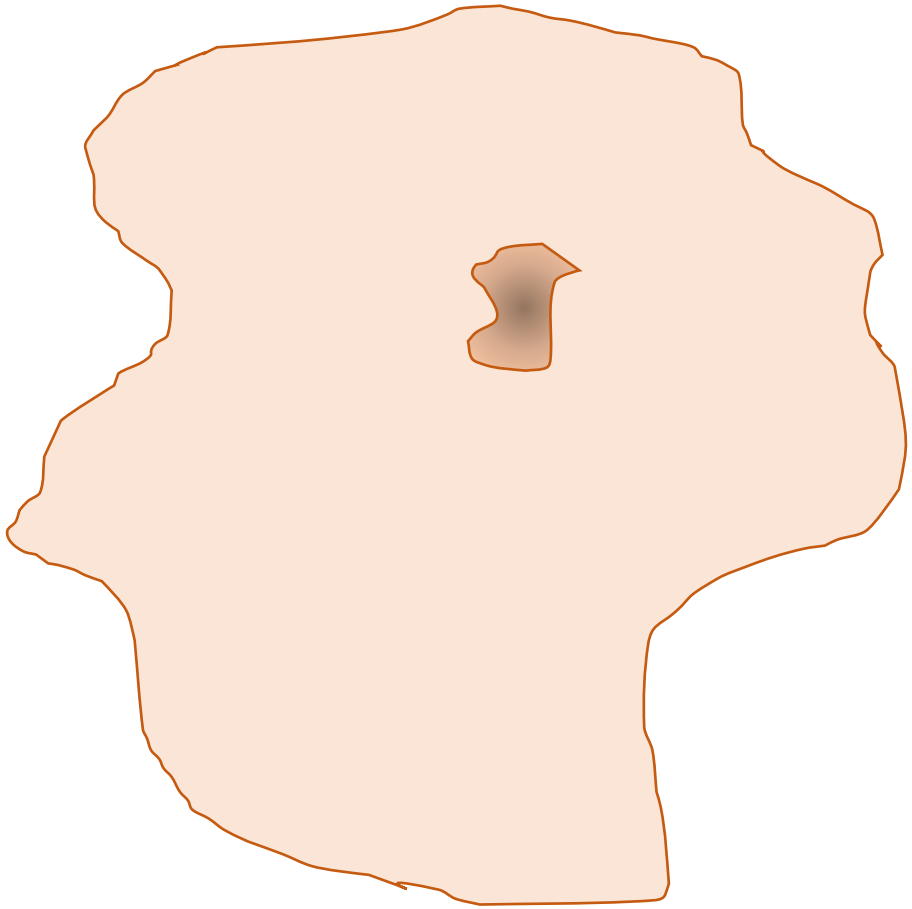
- synthetic analog of folic acid
  - amino group at C4 instead of OH
  - methyl group at N10 instead of an H

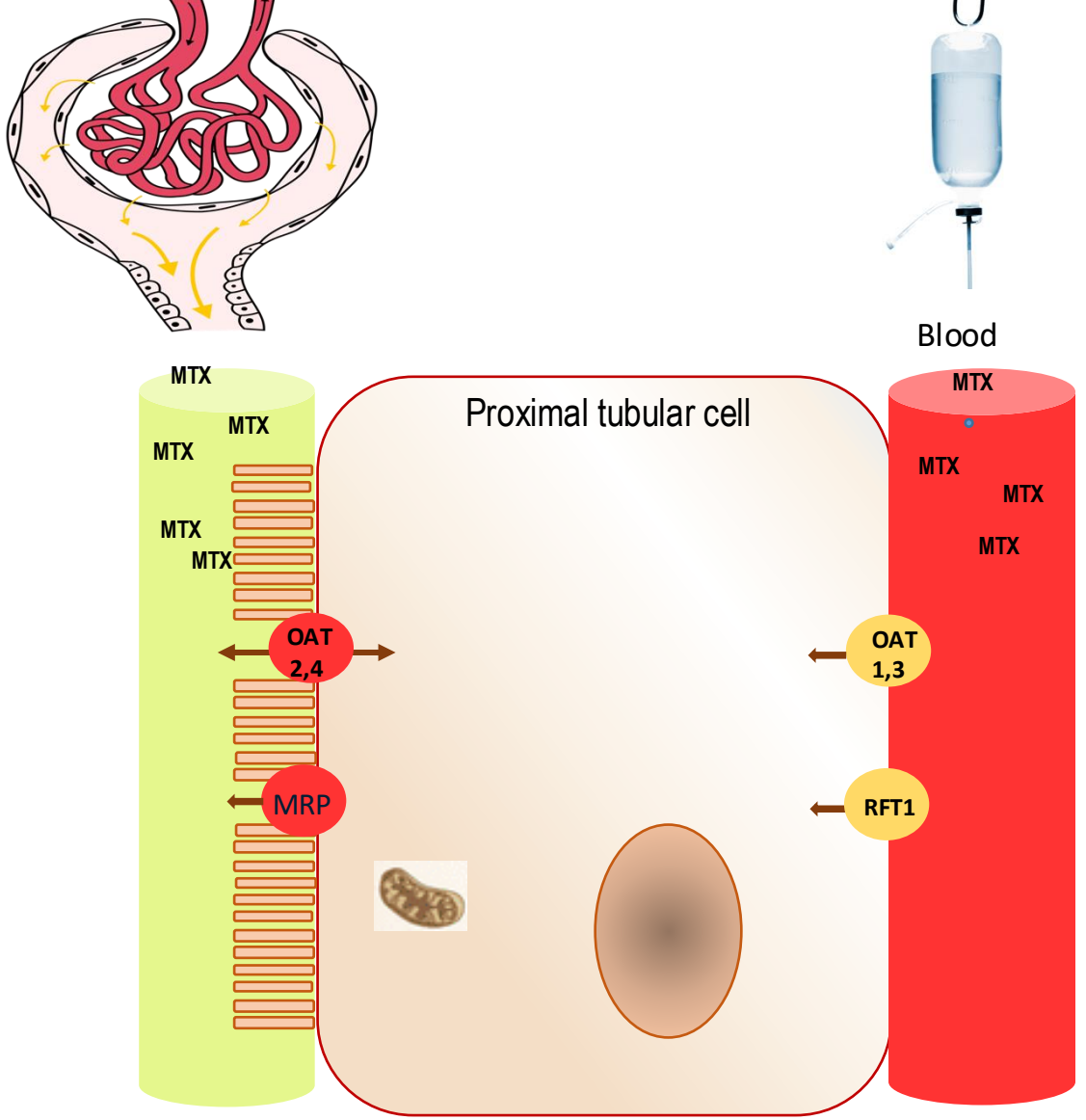
MOA of Methotrexate





Ayako Takeuchi et al. K Int 2001





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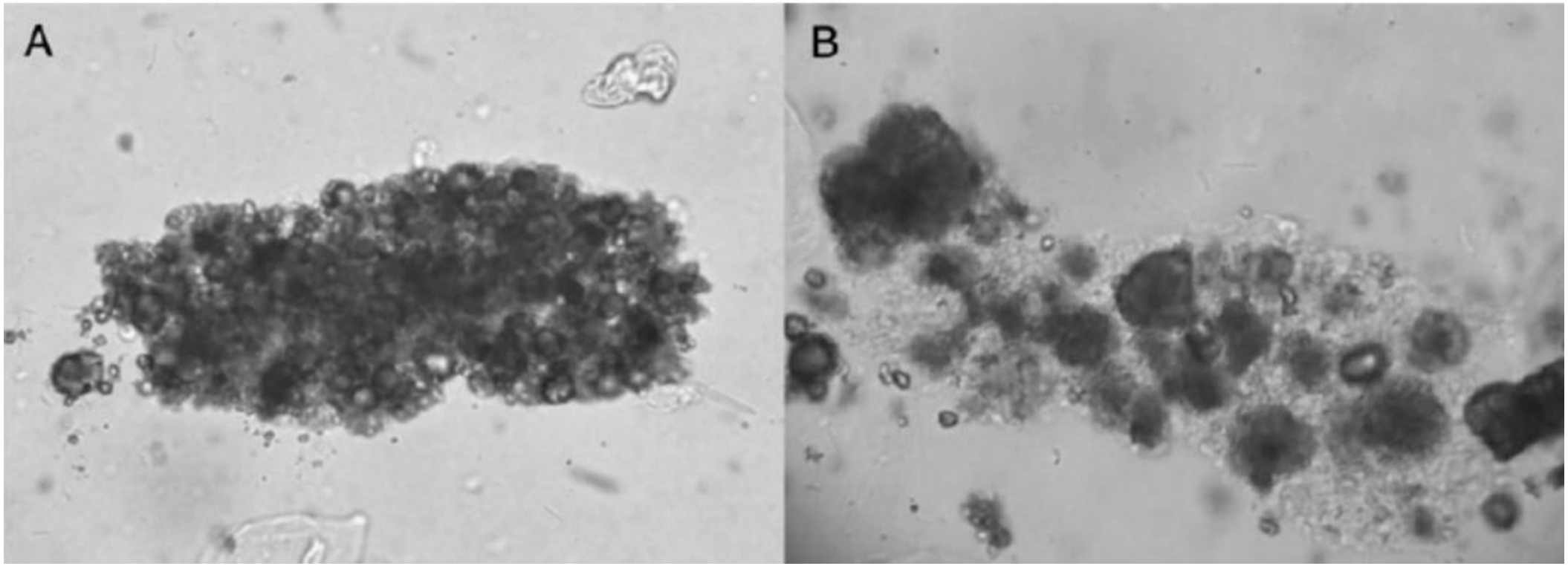

A
B

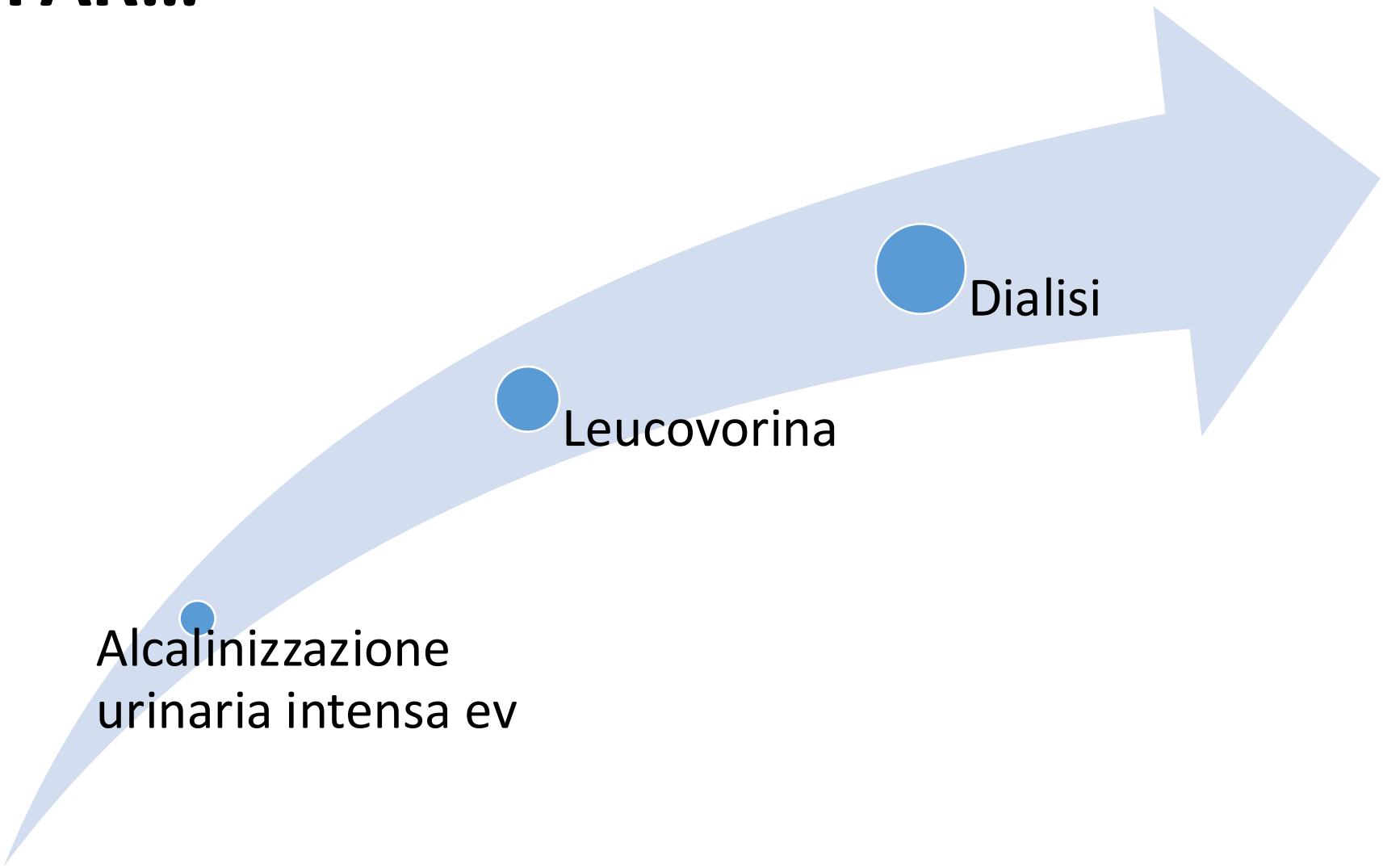
Risk factors

- Drug pharmacokinetics : **90% renal excretion within 24h as MTX**
- Inappropriate dose: **Distribution volume of MTX might be incorrect**
- Inaccurate renal function evaluation: **Current biomarkers might be inaccurate in cancer pts**
- Hyperhomocysteinemia: **It can be cause or effect**
- Concomitant administration of nephrotoxic or interfering agents: **PPI, NSAIDs, antibiotics, etc**
- Urinary pH : **Make sure and check UpH is ≥7 – even ≥8 if CKD**
- Risk of systemic toxicity in comorbidities: **CKD!!!**

To Do List

- [ ] Knowing MTX nephrotoxicity mechanisms
- [ ] How to prevent
- [x] How to treat

SO FAR…



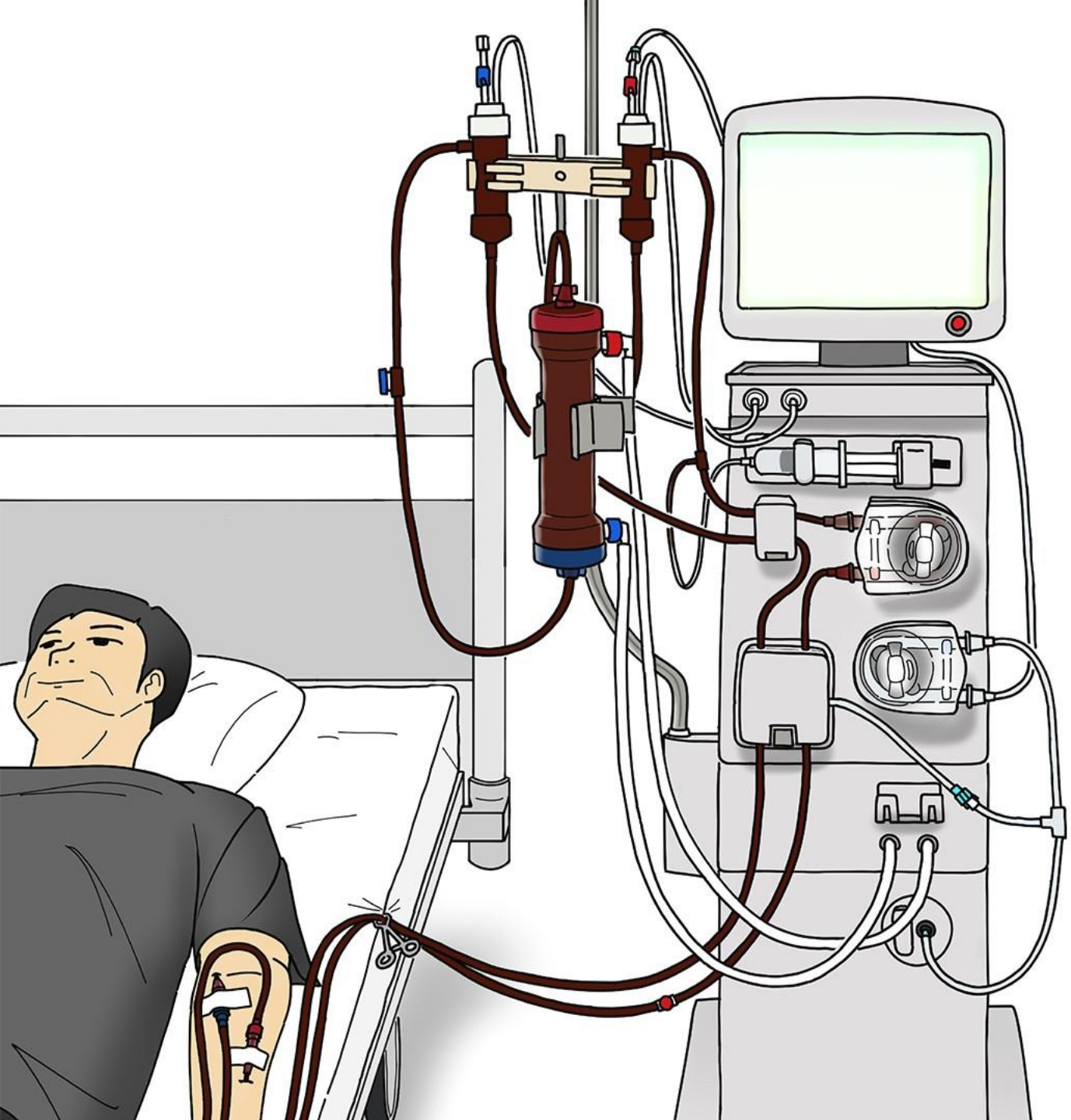
High mortality

No renal recovery

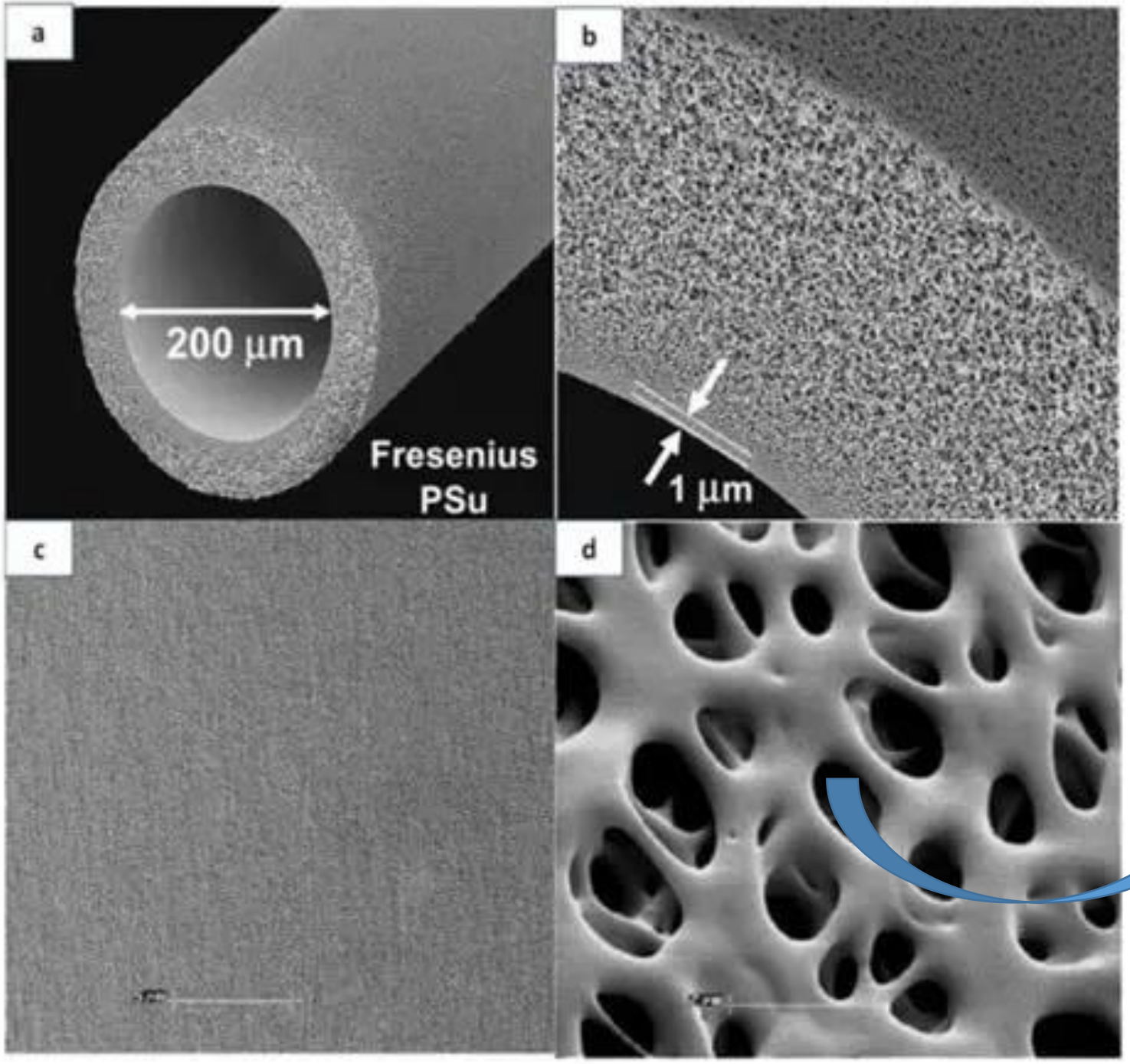
Long hospitalization

Therapy suspension

MTX FIGHTING



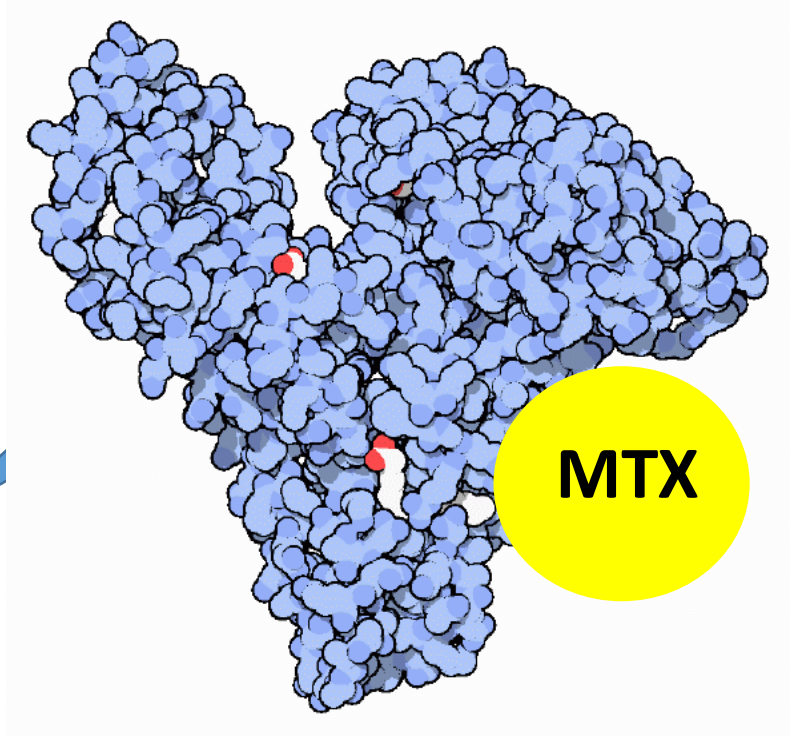
Is standard hemodialysis
able to effectively remove MTX?



MTX albumin binding: 50%

Albumin 69 kDA

Bore 400 A°



Svantaggi e rischi della terapia extracorporea

- Need for vascular access (CVC in giugular vein)
- Hemodynamic instability
- Need for anticoagulation
- Infectious risk
- Allergic risk
- Osmotic and electrolyte imbalance risk
- High cost
- Logistic problems
- Rebound effect
- Removal of Leucovorin

Front Med (Lausanne). 2025 Mar 14;12:1495705. doi: 10.3389/fmed.2025.1495705

High-flux hemodialysis as rescue therapy for high-dose methotrexate toxicity: case series and clinical insights

Ana Carolina Nakamura Tome [1,*], Karise Fernades Santos [1], Emerson Quintino Lima [1], Rodrigo Jose Ramalho [1]

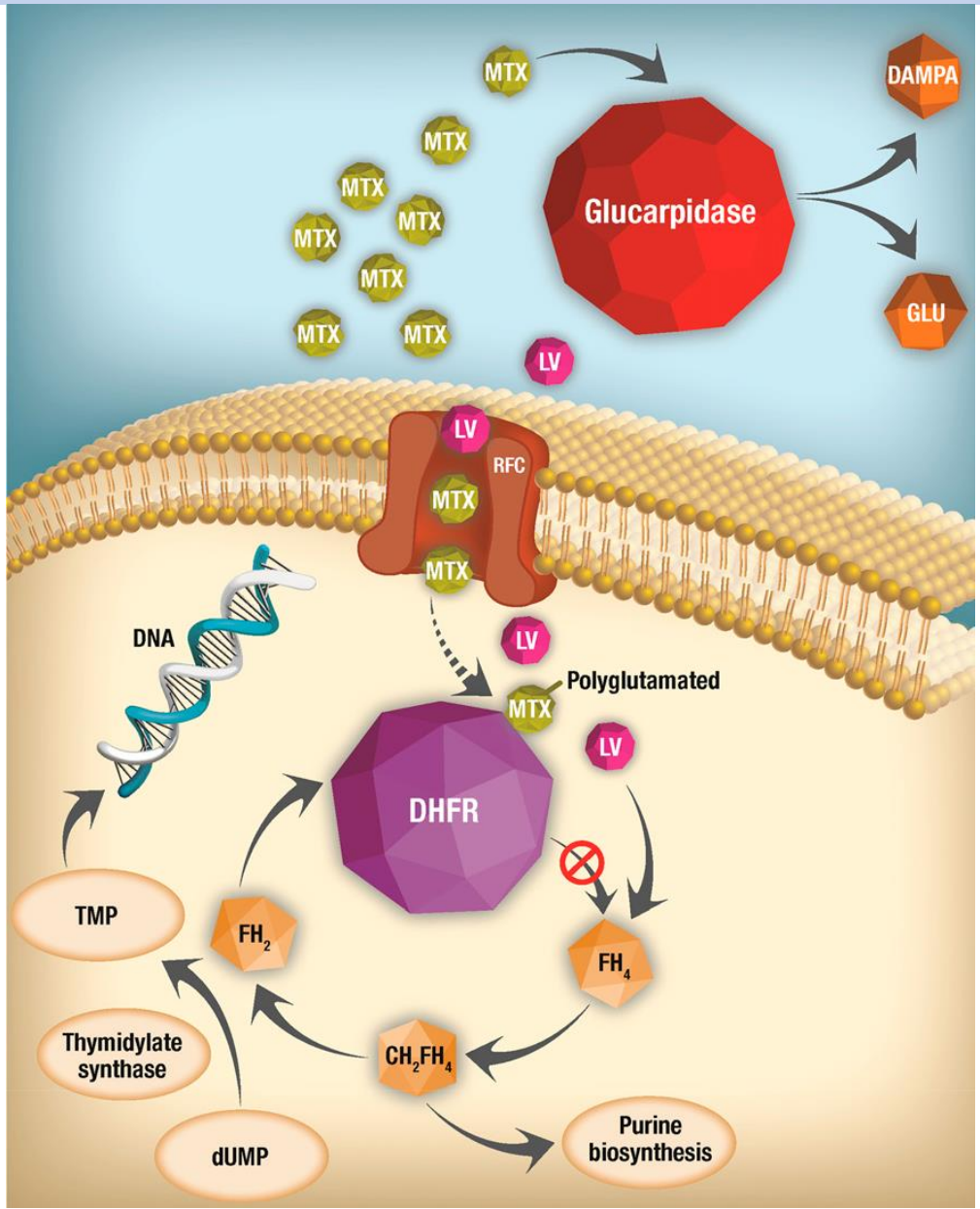
N=3 young pts

HF-HD sessions required were 5.3 ± 2.5

Mean relative reduction in serum methotrexate concentration was 44.5 ± 19.1%

In conclusion, for patients experiencing HD-MTX intoxication, when glucarpidase is unavailable, HF-HD presents an effective treatment option, with a lower cost compared to other extracorporeal therapies. Serum MTX rebound occurs, and repeated sessions may be necessary to ensure adequate patient management.

Glucarpidase



Reduction by ≥97–99% of plasma MTX within 15–30 min

CLINICAL TRIALS AND OBSERVATIONS | APRIL 24, 2025

Glucarpidase for treatment of high-dose methotrexate toxicity

Clinical Trials & Observations

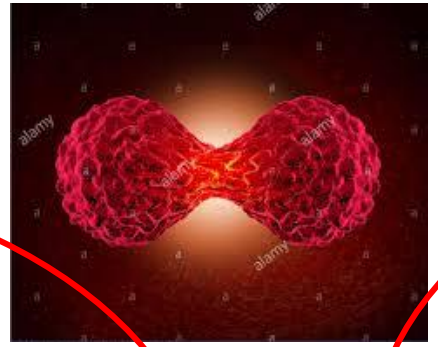
Shruti Gupta, Sarah A. Kaunfer, Kevin L. Chen, Julie-Alexia Dias, Anitha Vijayan, Arun Rajasekaran, Jason M. Prosek, Huong L. Truong,

Abstract

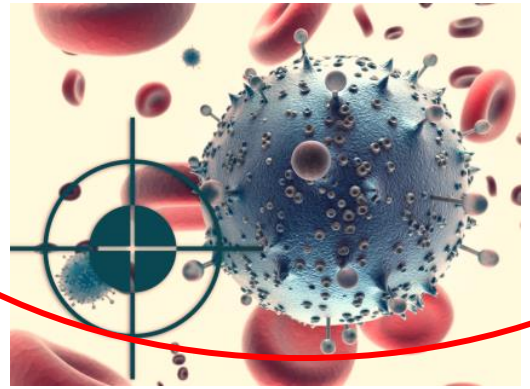
High-dose methotrexate (MTX) results in high rates of acute kidney injury (AKI), neutropenia, and hepatotoxicity. Glucarpidase is a recombinant enzyme that cleaves MTX, but clinical data supporting its use are scarce. We examined the association between glucarpidase administration and outcomes in adults with MTX-AKI from 28 cancer centers across the United States using a sequential target trial emulation framework. The primary end point was kidney recovery at hospital discharge, defined as survival to discharge with serum creatinine <1.5-fold baseline and without dialysis dependence. Key secondary end points were time to kidney recovery, neutropenia, and transaminitis on day 7, and time to death. Using multivariable logistic and Cox regression models, we compared outcomes in patients who received glucarpidase within 4 days following MTX initiation with those in patients who did not. Among 708 patients with MTX-AKI, 209 (29.5%) received glucarpidase. Overall, 183 (25.8%) had a primary end point event. Glucarpidase receipt was associated with a 2.70-fold higher adjusted odds of kidney recovery (95% confidence interval [CI], 1.69–4.31) compared with no glucarpidase receipt. Patients treated with glucarpidase also had faster time to kidney recovery (adjusted hazard ratio [aHR], 1.88; 95% CI, 1.18–3.33) and lower risks of grade ≥2 neutropenia (adjusted odds ratio [aOR], 0.50; 95% CI, 0.28–0.91) and grade ≥2 transaminitis (aOR, 0.50; 95% CI, 0.28–0.91) on day 7. There was no difference in time to death (aHR, 0.76; 95% CI, 0.49–1.18). These data suggest glucarpidase may improve both renal and extrarenal outcomes in patients with MTX-AKI.

Drugs in Oncology: Lenalidomide

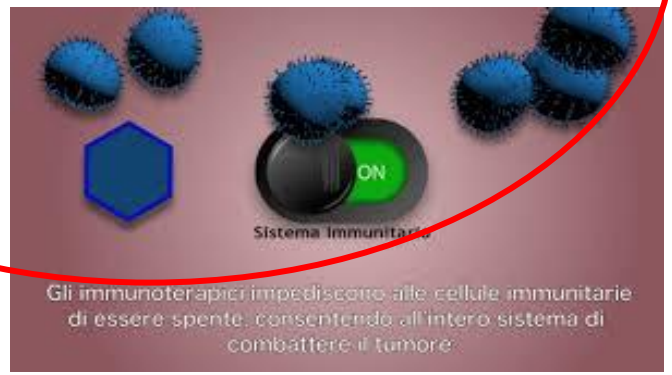
Cytotoxic Agents



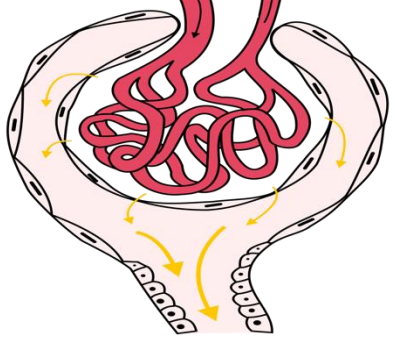
Targeted Chemiotherapic Agents

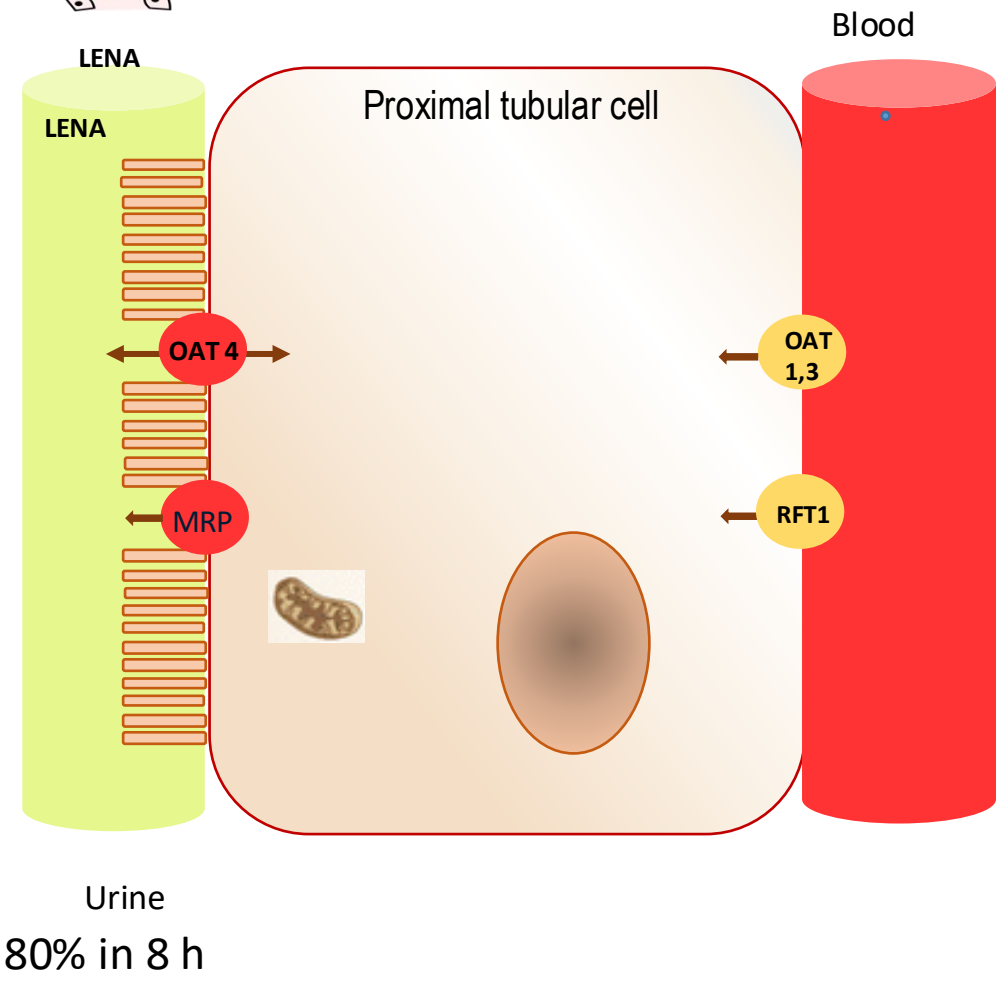


Immunotherapic Agents



eGFR 120 ml/min



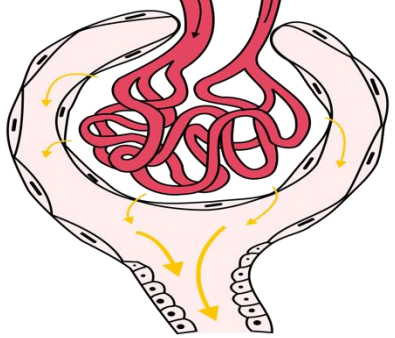


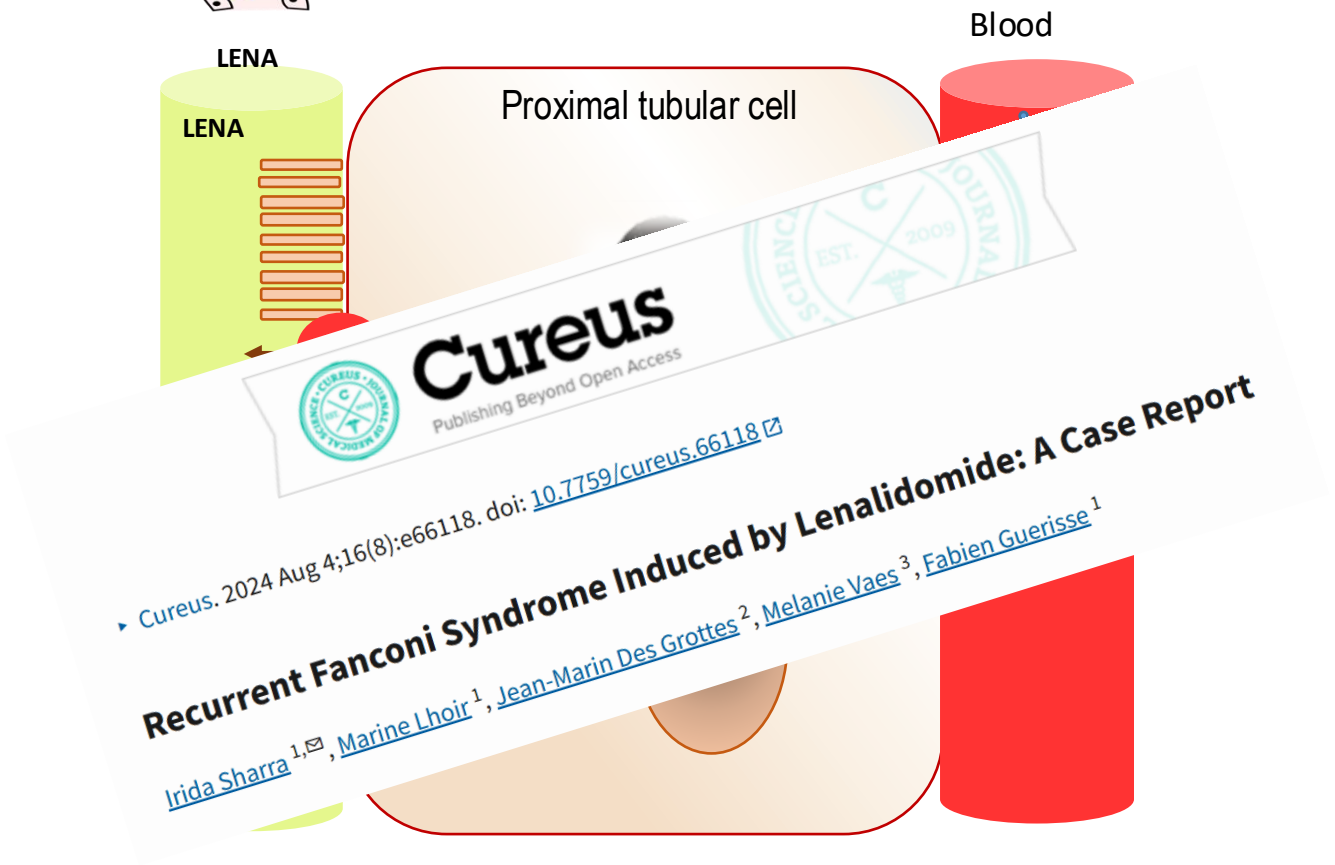
Urine

80% in 8 h

N. Chen et al. Clin Pharmachokin, 2007

eGFR ≤50 ml/min

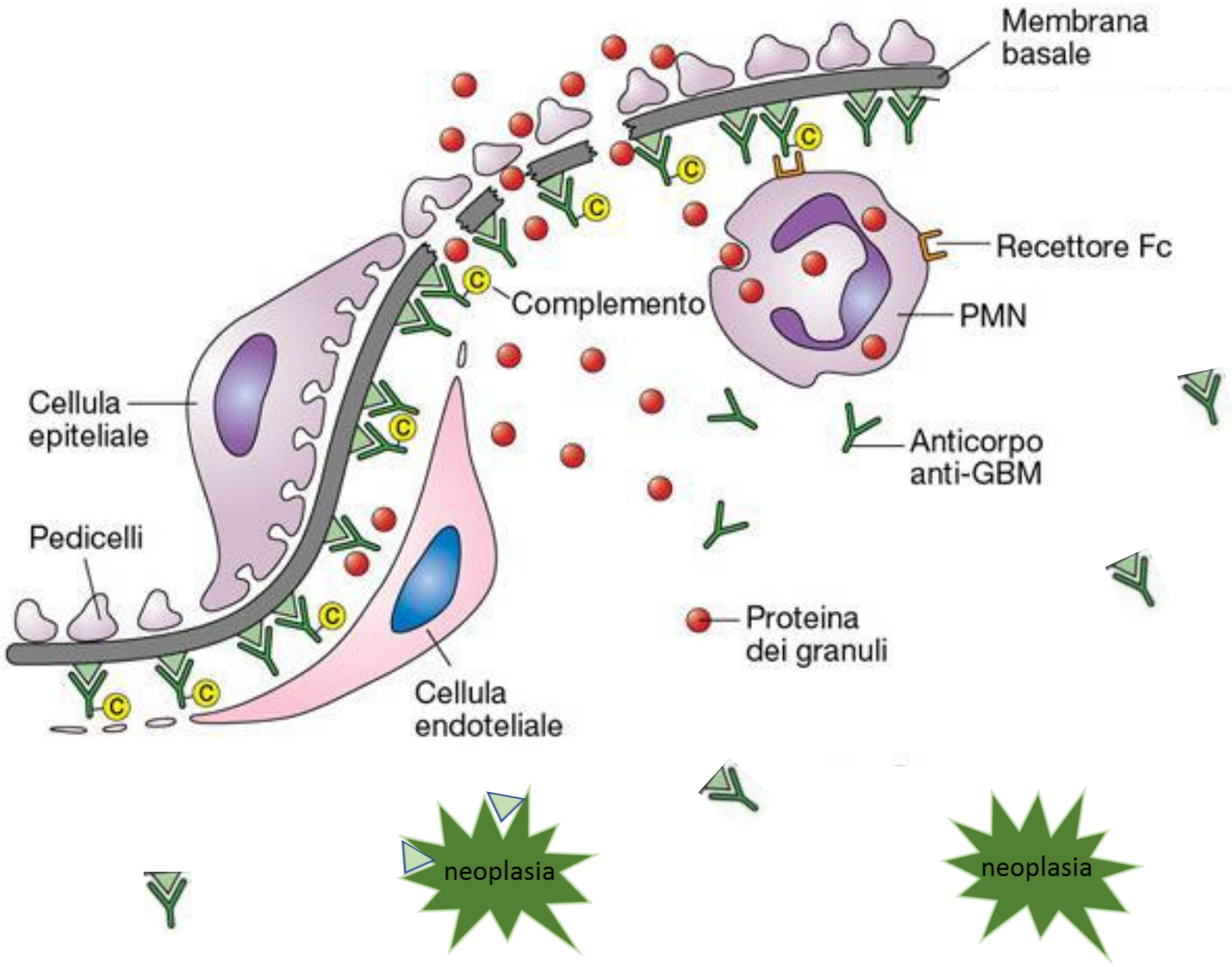




Urine

38-69% in 10 h

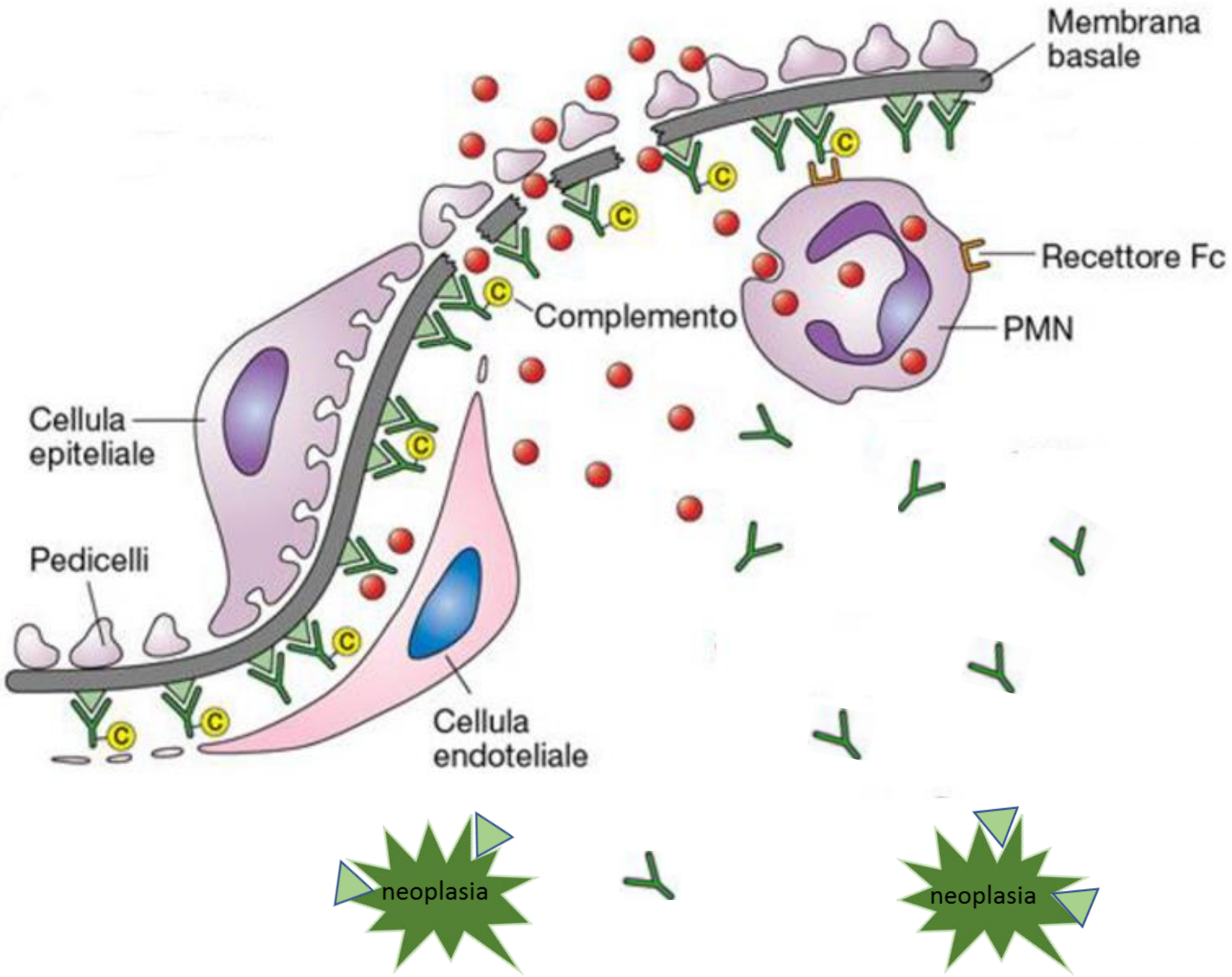
N. Chen et al. Clin Pharmachokin, 2007



Circulating immunocomplexes:

- The immune system responds to surface antigens expressed on the cell membrane on cancer cells by the production of antigen directed antibodies

- Immuno-complexes are produced in the blood and thereafter deposit in the glomerulus, were inflammation induces the damage of the glomerular barrier



Glomerulonephritis sustained by the formation of in situ immuno-complexes:

Cancer cells surface antigens might have structural similarities with glomerular membrane antigens

Immune system cross-reacts against glomerular antigens with antibodies formation that link with antigens and form immuno-complexes. Local inflammation induces the damage of the renal barrier.

Vascular-endothelial growth factor (VEGF) inhibition

Nephrotoxicity is mainly due to vascular effects

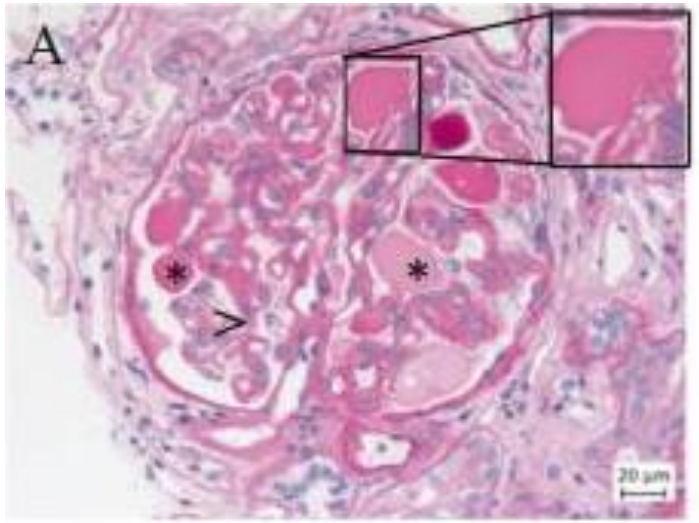
Ossidative stress
Endothelial dysfunction → Hypertension

Filtration barrier damage → Proteinuria

Proteinuria → - Nephrotic/Nephritic syndrome

Proteic Subendothelial accumulation → - Thrombotic microangiopathy

- AKI



Varsha et al. Am J Cancer Res (2020)

Conclusions

- Lymphomas treatment in old patients is a modern challenge in oncohematology
- Platinum-based drugs, HDMTX, Lenalidomide remain the nephrotoxic drugs which use can be very limited in old patients with lymphoma
- A preventive referral to the nephrologist will help mitigating drugs nephro- and systemic toxicity


Thank
You