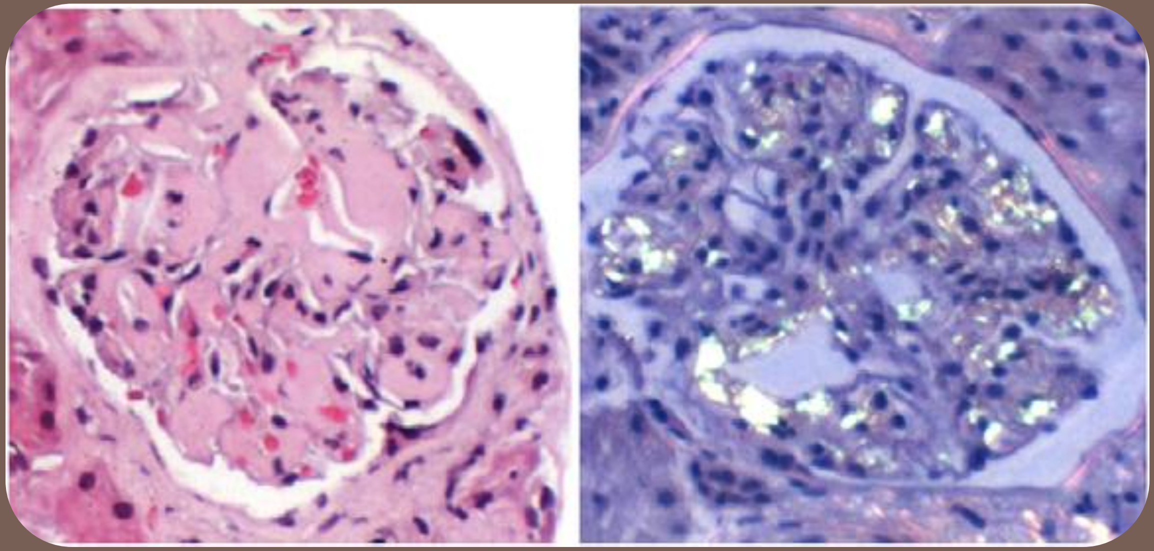
ONCO_NEFROLOGIA



Farmaci antiblastici e insufficienza renale

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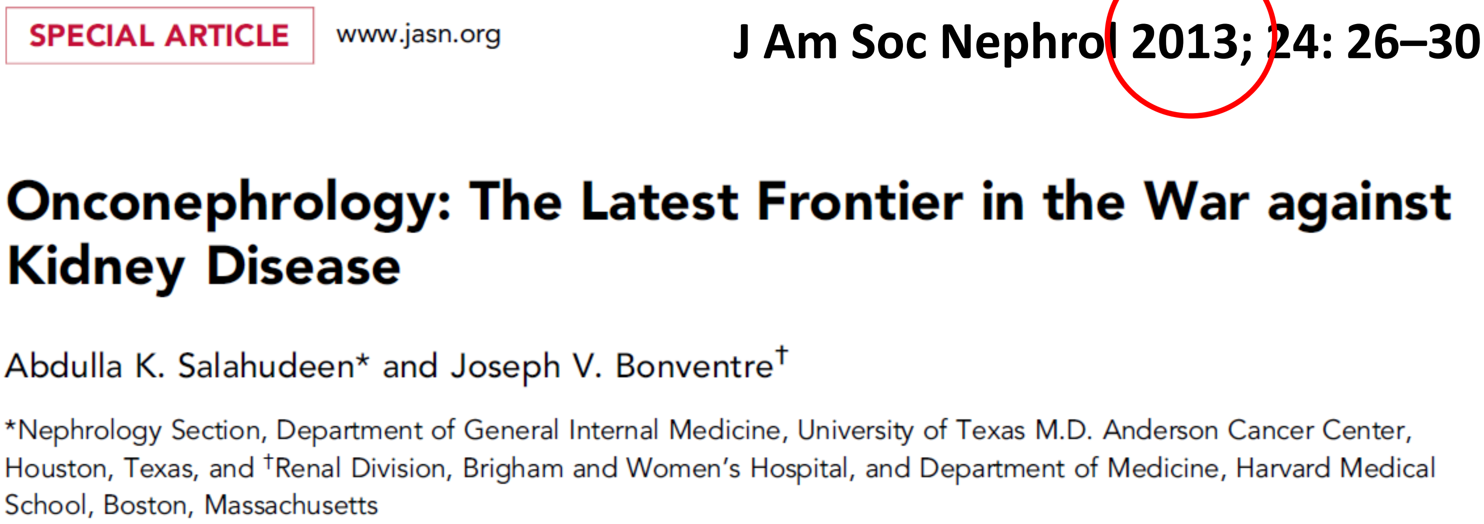

SPECIAL ARTICLE www.jasn.org

Onconephrology: The Latest Frontier in the War against Kidney Disease

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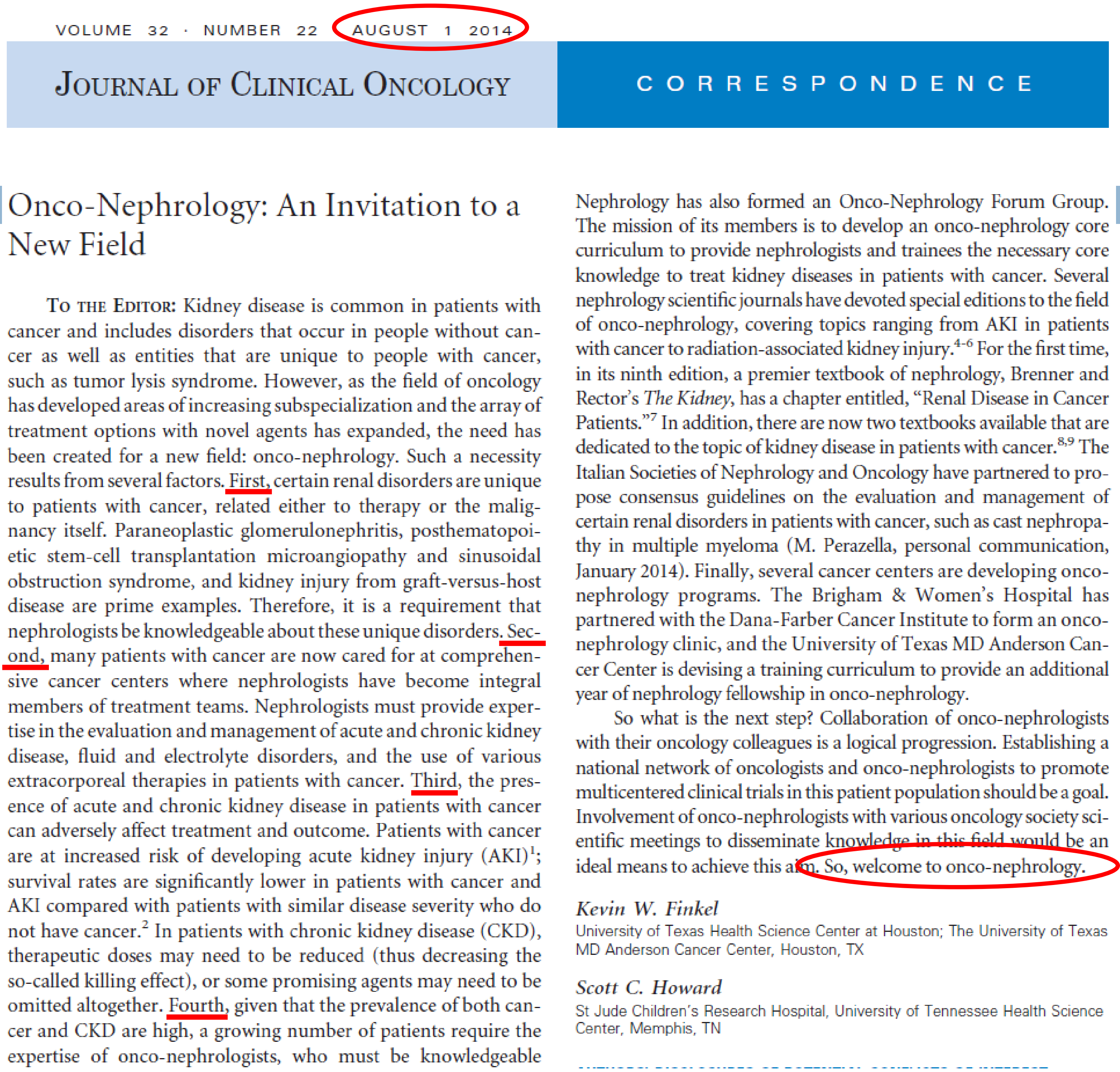
Il «Manifesto» del gruppo di onconefrologia della American Society of Nephrology



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CORRESPONDENCE

Onco-Nephrology: An Invitation to a New Field

To the Editor: Kidney disease is common in patients with cancer and includes disorders that occur in people without cancer as well as entities that are unique to people with cancer, such as tumor lysis syndrome. However, as the field of oncology has developed areas of increasing subspecialization and the array of treatment options with novel agents has expanded, the need has been created for a new field: onco-nephrology. Such a necessity results from several factors. First, certain renal disorders are unique to patients with cancer, related either to therapy or the malignancy itself. Paraneoplastic glomerulonephritis, posthematopoietic stem-cell transplantation microangiopathy and sinusoidal obstruction syndrome, and kidney injury from graft-versus-host disease are prime examples. Therefore, it is a requirement that nephrologists be knowledgeable about these unique disorders. Second, many patients with cancer are now cared for at comprehensive cancer centers where nephrologists have become integral members of treatment teams. Nephrologists must provide expertise in the evaluation and management of acute and chronic kidney disease, fluid and electrolyte disorders, and the use of various extracorporeal therapies in patients with cancer. Third, the presence of acute and chronic kidney disease in patients with cancer can adversely affect treatment and outcome. Patients with cancer are at increased risk of developing acute kidney injury (AKI)[1]; survival rates are significantly lower in patients with cancer and AKI compared with patients with similar disease severity who do not have cancer.[2] In patients with chronic kidney disease (CKD), therapeutic doses may need to be reduced (thus decreasing the so-called killing effect), or some promising agents may need to be omitted altogether. Fourth, given that the prevalence of both cancer and CKD are high, a growing number of patients require the expertise of onco-nephrologists, who must be knowledgeable Nephrology has also formed an Onco-Nephrology Forum Group. The mission of its members is to develop an onco-nephrology core curriculum to provide nephrologists and trainees the necessary core knowledge to treat kidney diseases in patients with cancer. Several nephrology scientific journals have devoted special editions to the field of onco-nephrology, covering topics ranging from AKI in patients with cancer to radiation-associated kidney injury.[4-6] For the first time, in its ninth edition, a premier textbook of nephrology, Brenner and Rector's *The Kidney*, has a chapter entitled, "Renal Disease in Cancer Patients."[7] In addition, there are now two textbooks available that are dedicated to the topic of kidney disease in patients with cancer.[8,9] The Italian Societies of Nephrology and Oncology have partnered to propose consensus guidelines on the evaluation and management of certain renal disorders in patients with cancer, such as cast nephropathy in multiple myeloma (M. Perazella, personal communication, January 2014). Finally, several cancer centers are developing onco-nephrology programs. The Brigham & Women's Hospital has partnered with the Dana-Farber Cancer Institute to form an onco-nephrology clinic, and the University of Texas MD Anderson Cancer Center is devising a training curriculum to provide an additional year of nephrology fellowship in onco-nephrology.

So what is the next step? Collaboration of onco-nephrologists with their oncology colleagues is a logical progression. Establishing a national network of oncologists and onco-nephrologists to promote multicentered clinical trials in this patient population should be a goal. Involvement of onco-nephrologists with various oncology society scientific meetings to disseminate knowledge in this field would be an ideal means to achieve this aim. So, welcome to onco-nephrology.

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Invito ad un nuovo campo d’azione : la onco-nefrologia

1) Certe patologie renali sono **esclusive** dei pazienti con cancro (glomerulonefrite paraneoplastica,microangiopatia post HSCT)
2) Il **nefrologo fa parte ormai dei team** dei dipartimenti di oncologia dei “Comprehensive Cancer Centers”
3) **AKI e CKD** sono più diffusi nella popolazione con cancro che nel resto della popolazione (25% di AKI nei pazienti trattati)
4) **Occorre saper riconoscere e gestire gli effetti collaterali in ambito renale dei chemioterapici e delle target therapies**
5) Ci sono sempre più **lungo- sopravviventi** al tumore, con problematiche renali croniche post-trattamenti

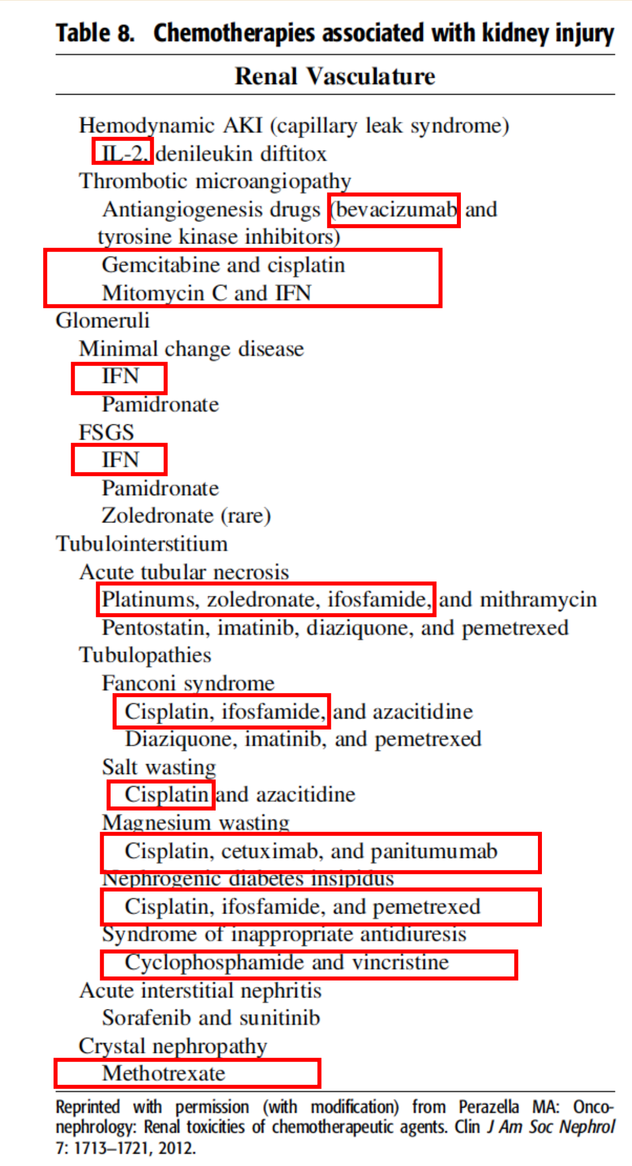


Table 8. Chemotherapies associated with kidney injury

Renal Vasculature

- Hemodynamic AKI (capillary leak syndrome)
  - IL-2, denileukin diftitox
- Thrombotic microangiopathy
  - Antiangiogenesis drugs (bevacizumab and tyrosine kinase inhibitors)
  - Gemcitabine and cisplatin
  - Mitomycin C and IFN

Glomeruli

- Minimal change disease
  - IFN
  - Pamidronate
- FSGS
  - IFN
  - Pamidronate
  - Zoledronate (rare)

Tubulointerstitium

- Acute tubular necrosis
  - Platinums, zoledronate, ifosfamide, and mithramycin
  - Pentostatin, imatinib, diaziquone, and pemetrexed
- Tubulopathies
  - Fanconi syndrome
    - Cisplatin, ifosfamide, and azacitidine
    - Diaziquone, imatinib, and pemetrexed
  - Salt wasting
    - Cisplatin and azacitidine
  - Magnesium wasting
    - Cisplatin, cetuximab, and panitumumab
  - Nephrogenic diabetes insipidus
    - Cisplatin, ifosfamide, and pemetrexed
  - Syndrome of inappropriate antidiuresis
    - Cyclophosphamide and vincristine
- Acute interstitial nephritis
  - Sorafenib and sunitinib
- Crystal nephropathy
  - Methotrexate

Reprinted with permission (with modification) from Perazella MA: Onco-nephrology: Renal toxicities of chemotherapeutic agents. Clin *J Am Soc Nephrol* 7: 1713–1721, 2012.

Perazella (Yale university) CJASN 7:1713-1721-2012

Fattori di rischio

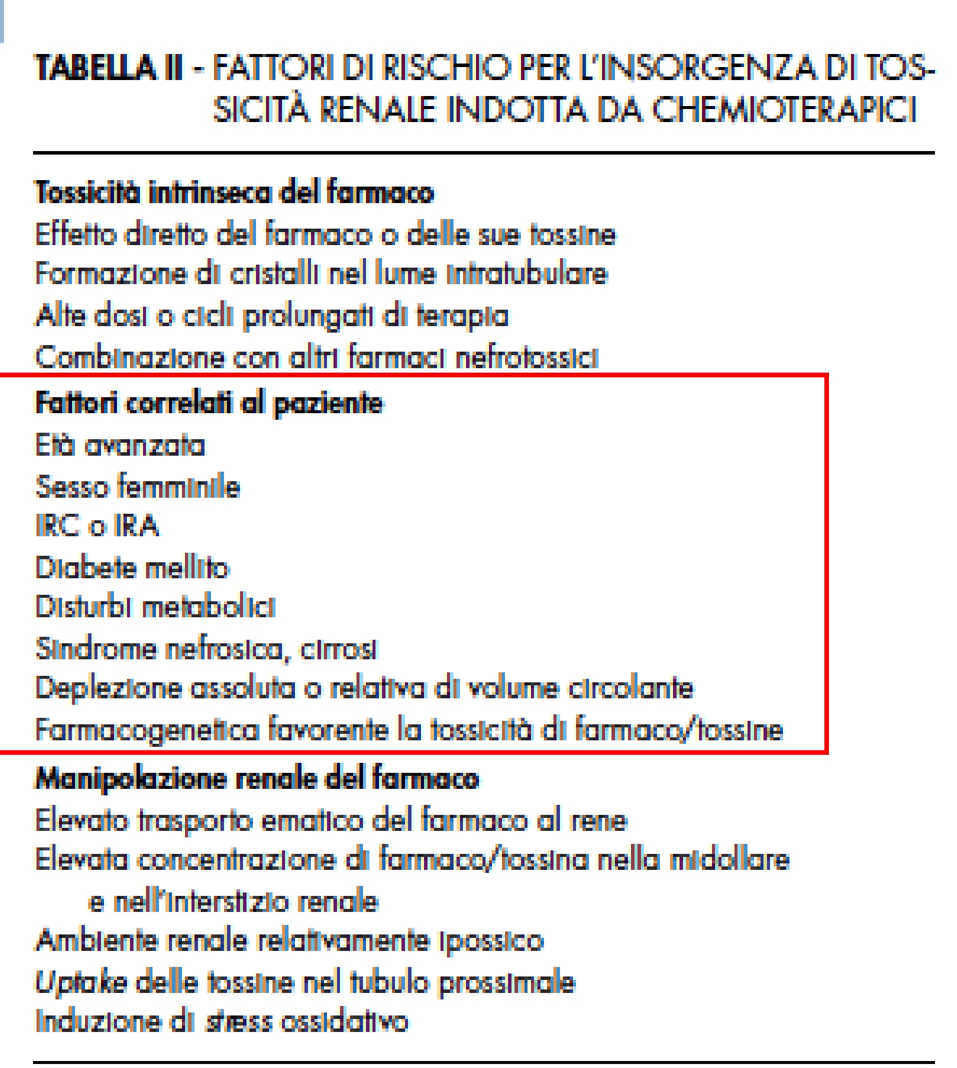


TABELLA II - FATTORI DI RISCHIO PER L'INSORGENZA DI TOSSICITÀ RENALE INDOTTA DA CHEMIOTERAPICI

Tossicità intrinseca del farmaco
Effetto diretto del farmaco o delle sue tossine
Formazione di cristalli nel lume intratubulare
Alte dosi o cicli prolungati di terapia
Combinazione con altri farmaci nefrotossici

Fattori correlati al paziente
Età avanzata
Sesso femminile
IRC o IRA
Diabete mellito
Disturbi metabolici
Sindrome nefrosica, cirrosi
Deplezione assoluta o relativa di volume circolante
Farmacogenetica favorente la tossicità di farmaco/tossine

Manipolazione renale del farmaco
Elevato trasporto ematico del farmaco al rene
Elevata concentrazione di farmaco/tossina nella midollare e nell'interstizio renale
Ambiente renale relativamente ipossico
Uptake delle tossine nel tubulo prossimale
Induzione di *stress* ossidativo

Suscettibilità renale agli agenti chemioterapici

A. **Non tutti i chemioterapici potenzialmente nefrotossici sviluppano uno screzio renale**
B. Attenzione alla **disidratazione** (nausea/vomito, diarrea, asciti e versamenti pleurici massivi ,sepsi, poliuria..)
C. **Alte dosi o dosi prolungate** : monitoraggio attento delle condizioni cliniche e dei fattori di rischio
D. **Età avanzata**: vi sono molti casi di depressione del GFR non riconosciuti, alte quote di stress ossidativo renale, eccessivi livelli di angiotensina II/endotelina
E. Eterogenea risposta agli agenti chemioterapici: **polimorfismo** nel sistema enzimatico del citocromo P450 renale !

Classificazione delle lesioni renali da chemioterapici

- Danno sulla vascolarizzazione renale e ed extrarenale : Microangiopatia trombotica (TMA) ➔ **bevacizumab, gemcitabina , mitomicina, bleomicina**
- Danno sul glomerulo : podocitopatia ➔ **IFN**
- Danno tubulare acuto ➔ **cisplatino , ifosfamide, pemetrexed**
- Danno tubulare cronico con perdita di magnesio ➔ **cetuximab**, **panitumumab**
- Danno tubulare con nefropatia da cristalli➔ **methotrexate**

“Pre-renal failure” in oncologia

Infusioni di **IL2** –**GCSF**- **gemcitabina** sono state associate con lo sviluppo dell’**SCLS** –**sistemic capillary leak syndrome**- caratterizzata da ricorrenti episodi di shock ipovolemici secondarial ai “**plasma shifts**” dallo spazio intravascolare a quello extravascolare : edema cardiaco, versamenti pleurici, ascite , versamento pericardico, ipotensione e deficit multi-organo (terapia di supporto con fluidi, diuretici e vasopressori , spesso letale)

Bevacizumab

- **Anticorpo anti VEGF**(vascular endothelial growth factor)
- VEGF è prodotto dalle cellule renali epiteliali viscerali , aggancia i **recettori localizzati sull'endotelio glomerulare** e dei **capillari peritubulari** : la produzione locale di VEGF mantiene la normale funzione di queste cellule , incluso il riparo dai danni transitori
- Effetti più noti: **ipertensione arteriosa , proteinuria** (20-40%) AKI (acute kidney injury) – lo sviluppo di ipertensione predice una miglior risposta
- Monitoraggio, idratazione adeguata, controllo della pressione arteriosa , adeguamento di dose
- Utile una terapia con **Ace inibitori** anche per la proteinuria

TMA : microangiopatia trombotica

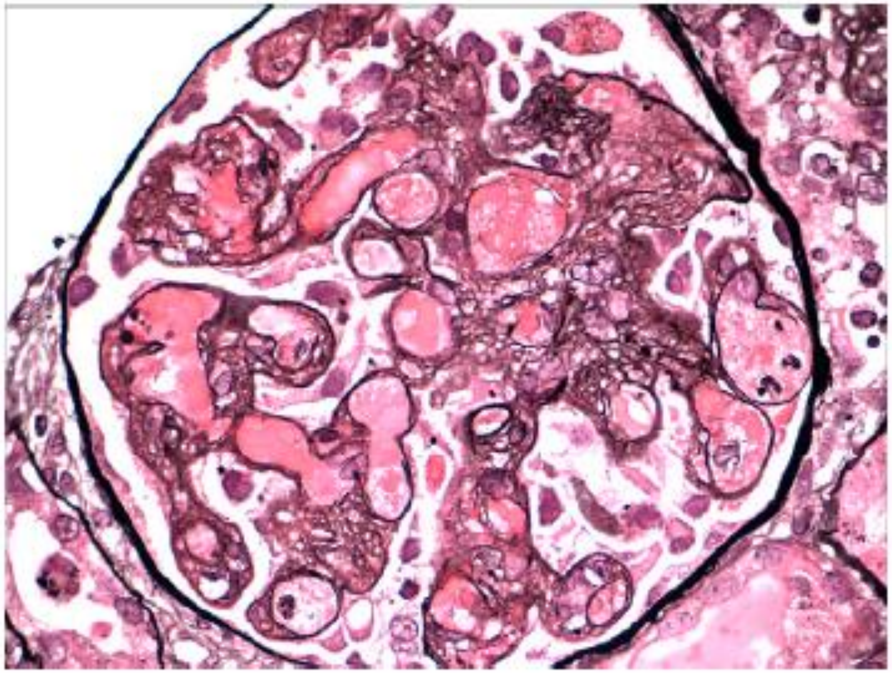


Figure 1. | **A glomerulus exhibits mesangiolysis, endothelial denudation, red blood cell congestion, and glomerular basement membrane duplication in this example of thrombotic microangiopathy.** (Jones methenamine silver stain; original magnification, ×600.) Courtesy of Glen S. Markowitz.

Gemcitabina , Mitomicina C, Bleomicina, Bevacizumab e **TMA**

- **Thrombotic Microangiopathy** : anemia emolitica microangiopatica , trombocitopenia , aumento dell' LDH, ematuria , proteinuria , insufficienza renale, manifestazioni neurologiche
- **Immunocomplessi circolanti** che danneggiano l'endotelio riscontrati nel circolo(mitomicina C)
- E' praticamente impossibile prevederla (talora preceduta da crisi ipertensive)
- Piu' frequente in caso di tumori tipo **adenocarcinomi mucino-secernenti(stomaco, polmone) e nei linfomi**
- Trattamento: sospensione del farmaco, terapia anti-ipertensiva adeguata, dialisi quando indicata
- Plasmaferesi (controversa)
- Corticosteroidi,eparina , antiaggreganti : non migliorano la sopravvivenza

IFN e podocitopatia renale

- L'IFN , Glicoproteina rilasciata da leucociti, fibroblasti, Tcell, NK cell in risposta ai patogeni, puo' provocare una **malattia renale da danno ai podociti** (tramite un recettore sui podociti ne altera la proliferazione cellulare e incrementa l'espressione della classe II antigenica MCHC)

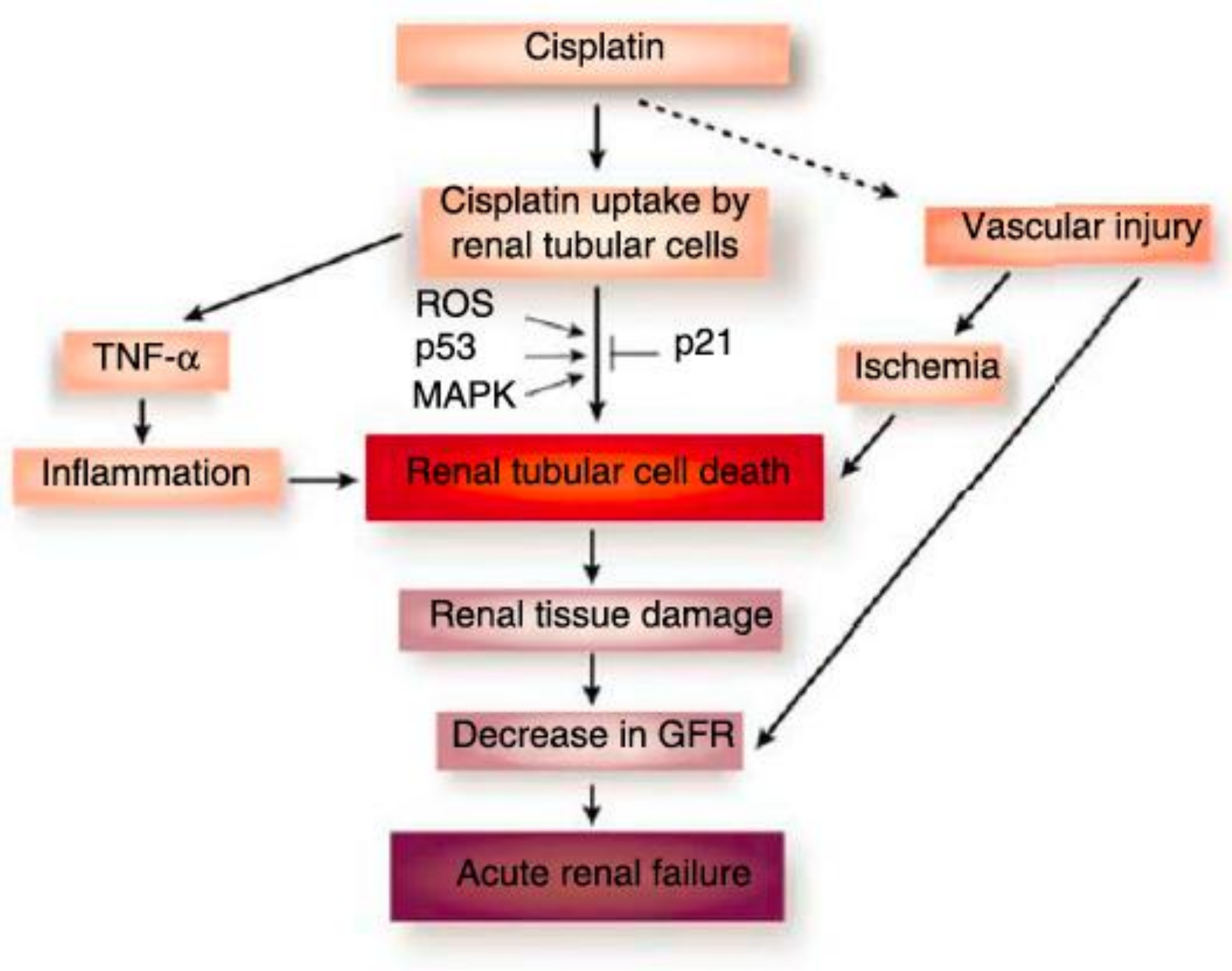
- *l'arteriola afferente penetra nella capsula di Bowman attraverso il suo polo vascolare e si ramifica in numerosi capillari fenestrati che descrivono una struttura la cui forma ricorda un gomitolo.*

La superficie esterna dei capillari è rivestita da podociti, cellule dotate di estroflessioni citoplasmatiche (dette pedicelli) che si interdigitano tra loro a formare un filtro in corrispondenza delle fenestrature.

Tra il rivestimento interno dei capillari e i pedicelli si trova la lamina densa, risultante dalla confluenza delle membrane basali dei podociti e delle cellule endoteliali-

- Sindrome nefrosica : interruzione del trattamento ; steroidi purtroppo non efficaci

Tossicità da Cisplatino

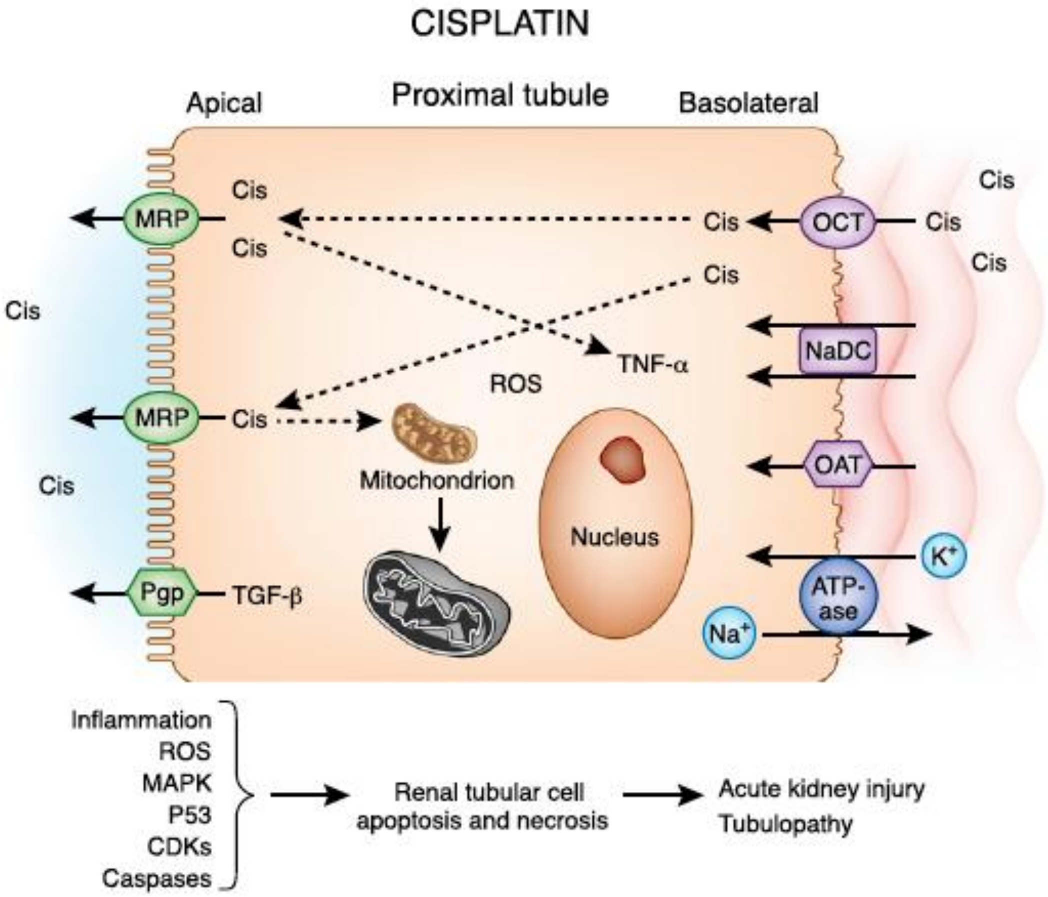


Cisplatin
Cisplatin uptake by renal tubular cells
Vascular injury
ROS
p53
MAPK
p21
TNF-α
Ischemia
Inflammation
Renal tubular cell death
Renal tissue damage
Decrease in GFR
Acute renal failure

Cisplatino e danno tubulare acuto

- **Nefrotossicità reversibile** (può diventare permanente se trascurata)
- Il Cloride alla posizione cis della molecola e' alla base della tossicità renale in quanto ne aumenta la concentrazione intracellulare renale nel **tubulo prossimale** (il carbossilato nel carboplatino e il ciclobutano nell'oxaliplatino no: nessuna delle due molecole è trasportata dall'OCT2-organic cation transporter 2-)
- Screzio renale, perdita di sodio, perdita di potassio, perdita di magnesio, proteinuria

Cisplatino e danno tubulare acuto


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

Da Perazella (Yale University)

Cisplatino e danno tubulare acuto

Trattamento :

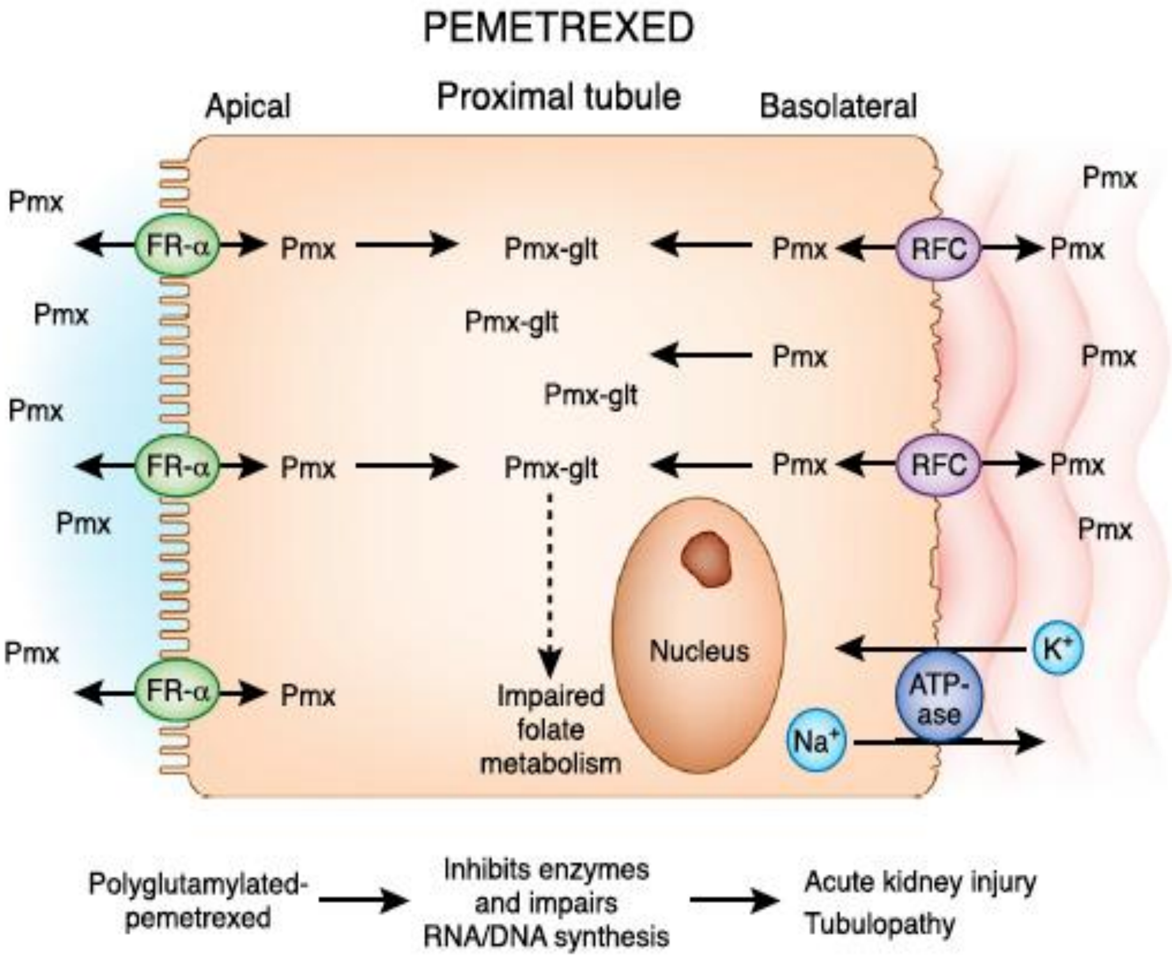
- **Diuresi forzata**
- **Idratazione**
- **supplemento di potassio e magnesio** parenterale

- Talora insorge la **sindrome di Fanconi** (fatale!): poliuria, glicosuria, iperfosfaturia, proteinuria, acidosi
- Amifostina e’ efficace nella prevenzione , ma l’insorgenza di sindrome di Stevens-Johnson ne ha molto limitato l’uso

Pemetrexed e danno tubulare

- Agente antifolato che inibisce gli enzimi coinvolti nel metabolismo di purina/pirimidina
- Viene escreto immodificato dal rene (70-90% in 24 h)
- Entra nelle cellule dei **tubuli prossimali** tramite il “ folate receptor-ɋ transport pathway” e dentro la cellula viene **poliglutammato** e non riesce piu’ a uscirne : a quel punto le alte concentrazioni intracellulari inibiscono il metabolismo enzimatico dei folati e comportano danno sul DNA-RNA cellulare
- AKI, proteinuria
- Trattamento: Discontinuazione del farmaco, idratazione
- necessaria profilassi con folati

Pemetrexed e danno tubulare

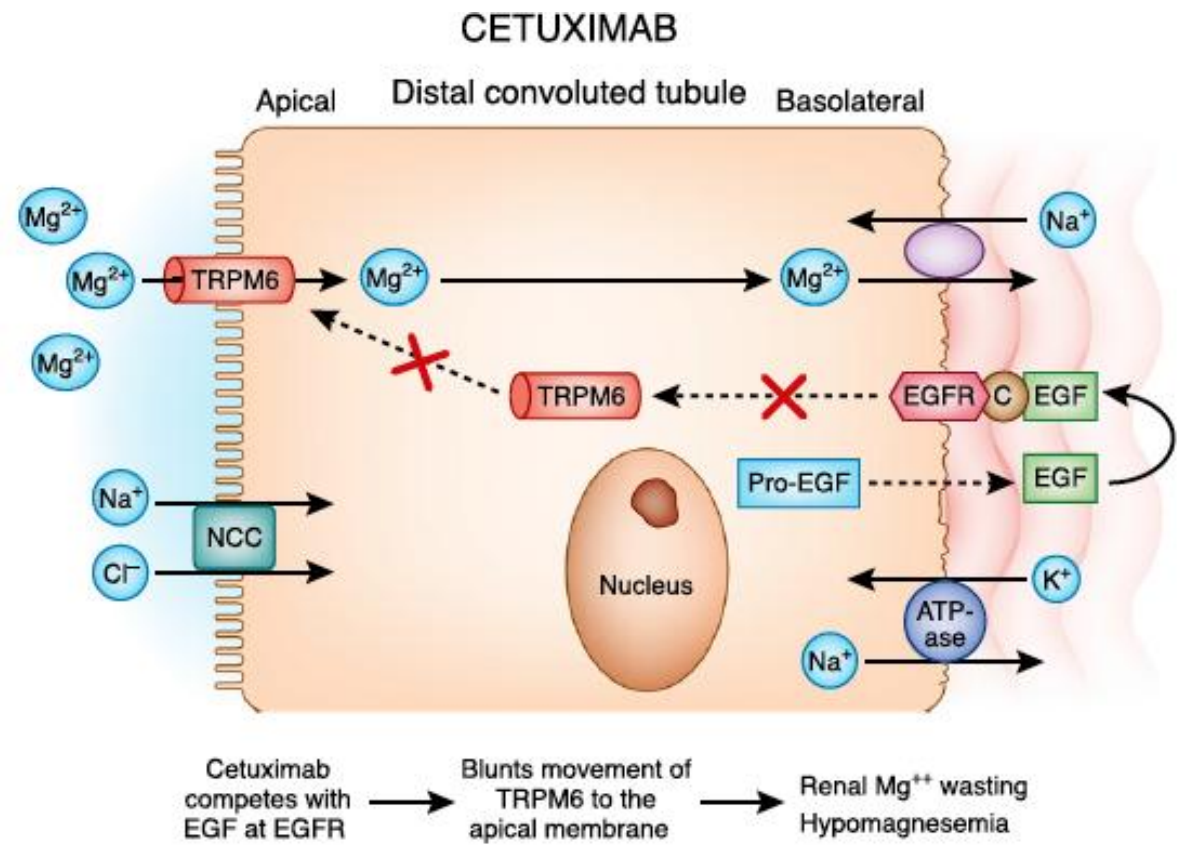

PEMETREXED
Apical
Proximal tubule
Basolateral
Pmx
FR-α
Pmx
Pmx-glt
Pmx
RFC
Pmx
Pmx
Pmx-glt
Pmx
Pmx
Pmx-glt
Pmx
FR-α
Pmx
Pmx-glt
Pmx
RFC
Pmx
Pmx
Pmx
Pmx
FR-α
Pmx
Impaired folate metabolism
Nucleus
K+
ATP-ase
Na+
Polyglutamylated-pemetrexed
Inhibits enzymes and impairs RNA/DNA synthesis
Acute kidney injury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

Da Perazella(Yale University)

Cetuximab e perdita di magnesio

- Cetuximab e’ un anticorpo contro EGFR (epithelial growth factor receptor)
- Il danno è nel **tubulo distale** convoluto : nella membrana basolaterale ci sono recettori per l’EGF : l’attivazione di essi stimola il TRPM6(transient receptor potential M6) a muoversi verso la parte apicale della membrana, il che facilita il riassorbimento del magnesio
- Il cetuximab inibisce il legame tra EGF e il suo recettore
- nel 2-6% delle casistiche si apprezza ipomagnesemia significativa (ma occorre monitorare con regolarità il dato)
- tossicità renale riscontrata anche per il panitumumab

Cetuximab e “magnesium wasting”


CETUXIMAB
Apical
Distal convoluted tubule
Basolateral
Mg2+
Mg2+
TRPM6
Mg2+
Mg2+
Mg2+
Na+
TRPM6
EGFR
C
EGF
Pro-EGF
EGF
Na+
NCC
Cl−
Nucleus
K+
ATP-ase
Na+
Cetuximab competes with EGF at EGFR
Blunts movement of TRPM6 to the apical membrane
Renal Mg++ wasting
Hypomagnesemia

Da Perazella(Yale university)

MTX e nefropatia da cristalli

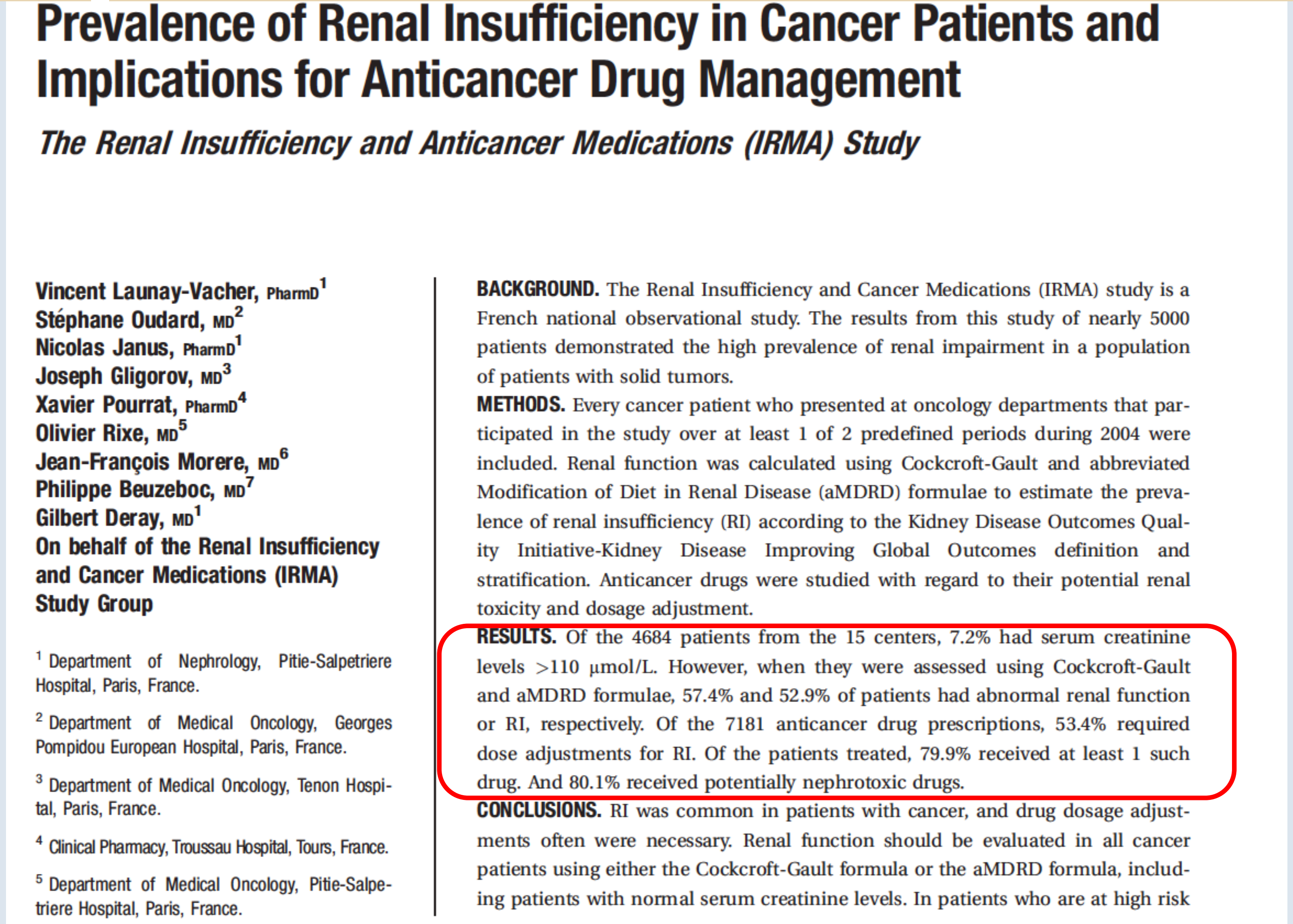
- Inibitore della di-idrofolati reduttasi
- Il suo metabolita maggiore -**7OH methotrexate**- e’ filtrato dai glomeruli e secreto dai tubuli prossimali : il problema deriva dal fatto che precipita nel lume dei tubuli distali
- Fattori di rischio: disidratazione con basso flusso urinario , ph acido delle urine, precedente di malattia renale
- Dosi appropiate !
- **Alcalinizzazione delle urine**
- Leucovorin rescue

Ifosfamide e danno tubulare acuto

- Danno sul **tubulo prossimale**
- Diabete insipido nefrogenico
- La diversa tossicita' della ifosfamide(nefrotossicita') rispetto alla ciclofosfamide (cistite emorragica) dipende dai loro metaboliti: l'**acroleina** della CTX non e' nefrotossica mentre la **cloroacetaldeide** derivata dall'IFO provoca danno renale – comporta deplezione del glutatione cellulare (l'IFO entra nelle cellule del tubulo prossimale tramite OCT2, la CTX no)
- Si usa il Mesna per prevenire la cistite emorragica (nel caso di dosaggi elevati, che sono la regola) ; non e' protettivo contro la nefropatia

TLS : tumor lysis syndrome

- Trattamento del Burkitt e LMA
- La distruzione cellulare immette in circolo in gran quantità acidi nucleici, fosforo e potassio ; gli **acidi nucleici** vengono **metabolizzati dall'enzima epatico xantina-ossidasi** con rapida escalation dell'acido urico sierico
- **L'acido urico** precipita nei tubuli renali creando ostruzione meccanica e stimolando una forte reazione infiammatoria che comporta ulteriore nefrotossicità
- Iperuricemia, iperkaliemia, iperfosfatemia, ipocalcemia
- Idratazione , **allopurinolo** (rasburicase se per via parenterale)
- Utilizzo di sodio bicarbonato solo se severa acidosi (può provocare depositi di calcio fosfato)



Prevalence of Renal Insufficiency in Cancer Patients and Implications for Anticancer Drug Management

The Renal Insufficiency and Anticancer Medications (IRMA) Study

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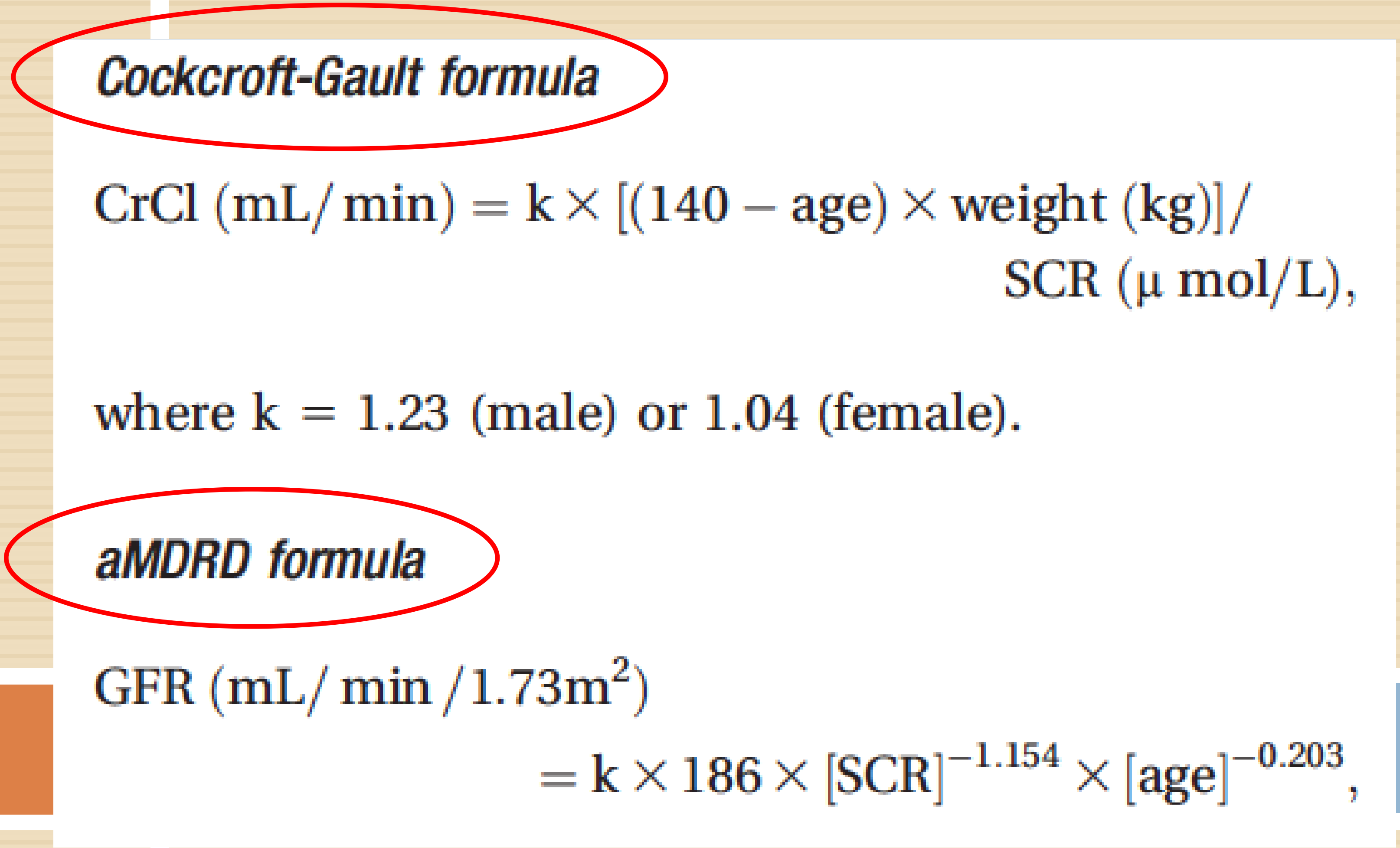
BACKGROUND. The Renal Insufficiency and Cancer Medications (IRMA) study is a French national observational study. The results from this study of nearly 5000 patients demonstrated the high prevalence of renal impairment in a population of patients with solid tumors.

METHODS. Every cancer patient who presented at oncology departments that participated in the study over at least 1 of 2 predefined periods during 2004 were included. Renal function was calculated using Cockcroft-Gault and abbreviated Modification of Diet in Renal Disease (aMDRD) formulae to estimate the prevalence of renal insufficiency (RI) according to the Kidney Disease Outcomes Quality Initiative-Kidney Disease Improving Global Outcomes definition and stratification. Anticancer drugs were studied with regard to their potential renal toxicity and dosage adjustment.

RESULTS. Of the 4684 patients from the 15 centers, 7.2% had serum creatinine levels >110 μmol/L. However, when they were assessed using Cockcroft-Gault and aMDRD formulae, 57.4% and 52.9% of patients had abnormal renal function or RI, respectively. Of the 7181 anticancer drug prescriptions, 53.4% required dose adjustments for RI. Of the patients treated, 79.9% received at least 1 such drug. And 80.1% received potentially nephrotoxic drugs.

CONCLUSIONS. RI was common in patients with cancer, and drug dosage adjustments often were necessary. Renal function should be evaluated in all cancer patients using either the Cockcroft-Gault formula or the aMDRD formula, including patients with normal serum creatinine levels. In patients who are at high risk

Cancer 2007; 110:1376-84



Cockcroft-Gault formula

$$\mathrm{CrCl}\ (\mathrm{mL/\min}) = k \times [(140 - \mathrm{age}) \times \mathrm{weight}\ (\mathrm{kg})] / \mathrm{SCR}\ (\mu\,\mathrm{mol/L}),$$

where $k = 1.23$ (male) or 1.04 (female).

aMDRD formula

$$\mathrm{GFR}\ (\mathrm{mL/\min}/1.73\mathrm{m}^2) = k \times 186 \times [\mathrm{SCR}]^{-1.154} \times [\mathrm{age}]^{-0.203},$$

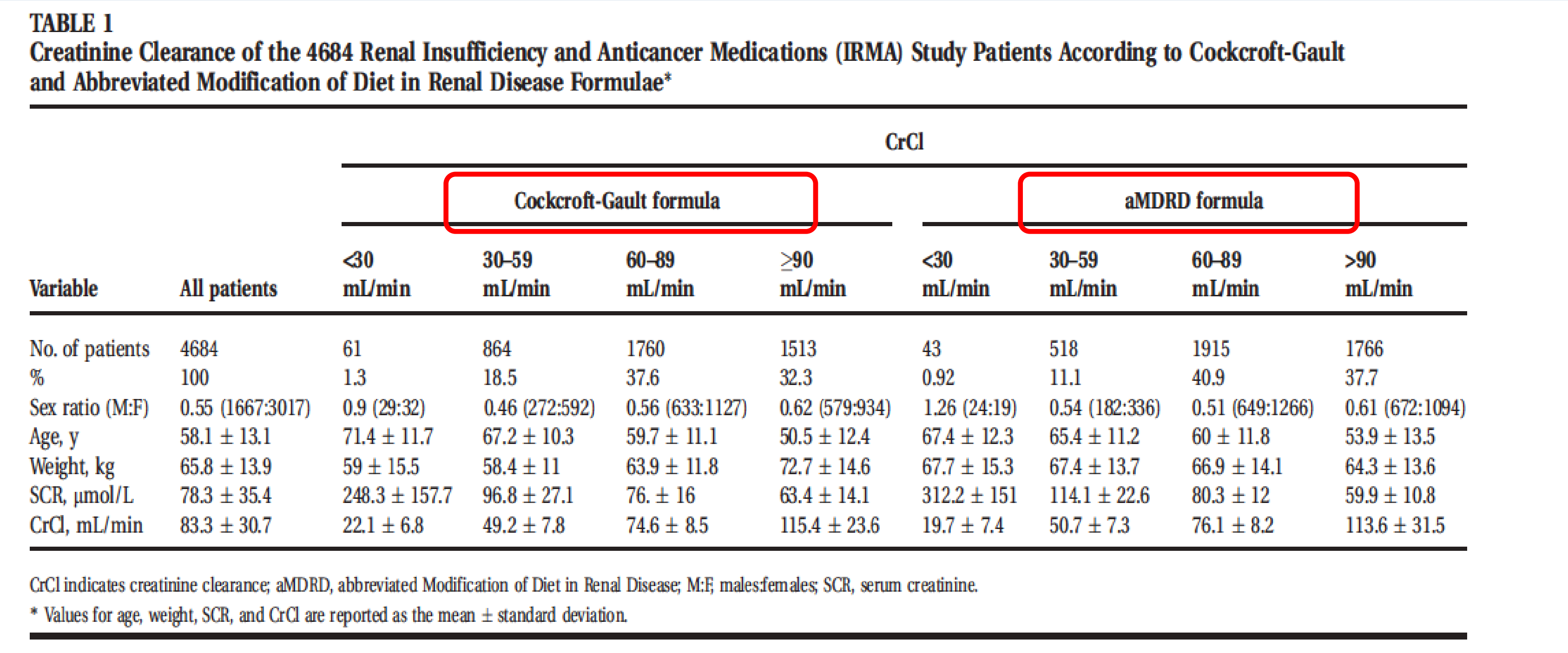


TABLE 1
Creatinine Clearance of the 4684 Renal Insufficiency and Anticancer Medications (IRMA) Study Patients According to Cockcroft-Gault and Abbreviated Modification of Diet in Renal Disease Formulae*

		CrCl							
		Cockcroft-Gault formula				aMDRD formula			
Variable	**All patients**	**<30 mL/min**	**30–59 mL/min**	**60–89 mL/min**	**≥90 mL/min**	**<30 mL/min**	**30–59 mL/min**	**60–89 mL/min**	**>90 mL/min**
No. of patients	4684	61	864	1760	1513	43	518	1915	1766
%	100	1.3	18.5	37.6	32.3	0.92	11.1	40.9	37.7
Sex ratio (M:F)	0.55 (1667:3017)	0.9 (29:32)	0.46 (272:592)	0.56 (633:1127)	0.62 (579:934)	1.26 (24:19)	0.54 (182:336)	0.51 (649:1266)	0.61 (672:1094)
Age, y	58.1 ± 13.1	71.4 ± 11.7	67.2 ± 10.3	59.7 ± 11.1	50.5 ± 12.4	67.4 ± 12.3	65.4 ± 11.2	60 ± 11.8	53.9 ± 13.5
Weight, kg	65.8 ± 13.9	59 ± 15.5	58.4 ± 11	63.9 ± 11.8	72.7 ± 14.6	67.7 ± 15.3	67.4 ± 13.7	66.9 ± 14.1	64.3 ± 13.6
SCR, µmol/L	78.3 ± 35.4	248.3 ± 157.7	96.8 ± 27.1	76. ± 16	63.4 ± 14.1	312.2 ± 151	114.1 ± 22.6	80.3 ± 12	59.9 ± 10.8
CrCl, mL/min	83.3 ± 30.7	22.1 ± 6.8	49.2 ± 7.8	74.6 ± 8.5	115.4 ± 23.6	19.7 ± 7.4	50.7 ± 7.3	76.1 ± 8.2	113.6 ± 31.5

CrCl indicates creatinine clearance; aMDRD, abbreviated Modification of Diet in Renal Disease; M:F, males:females; SCR, serum creatinine.

* Values for age, weight, SCR, and CrCl are reported as the mean ± standard deviation.

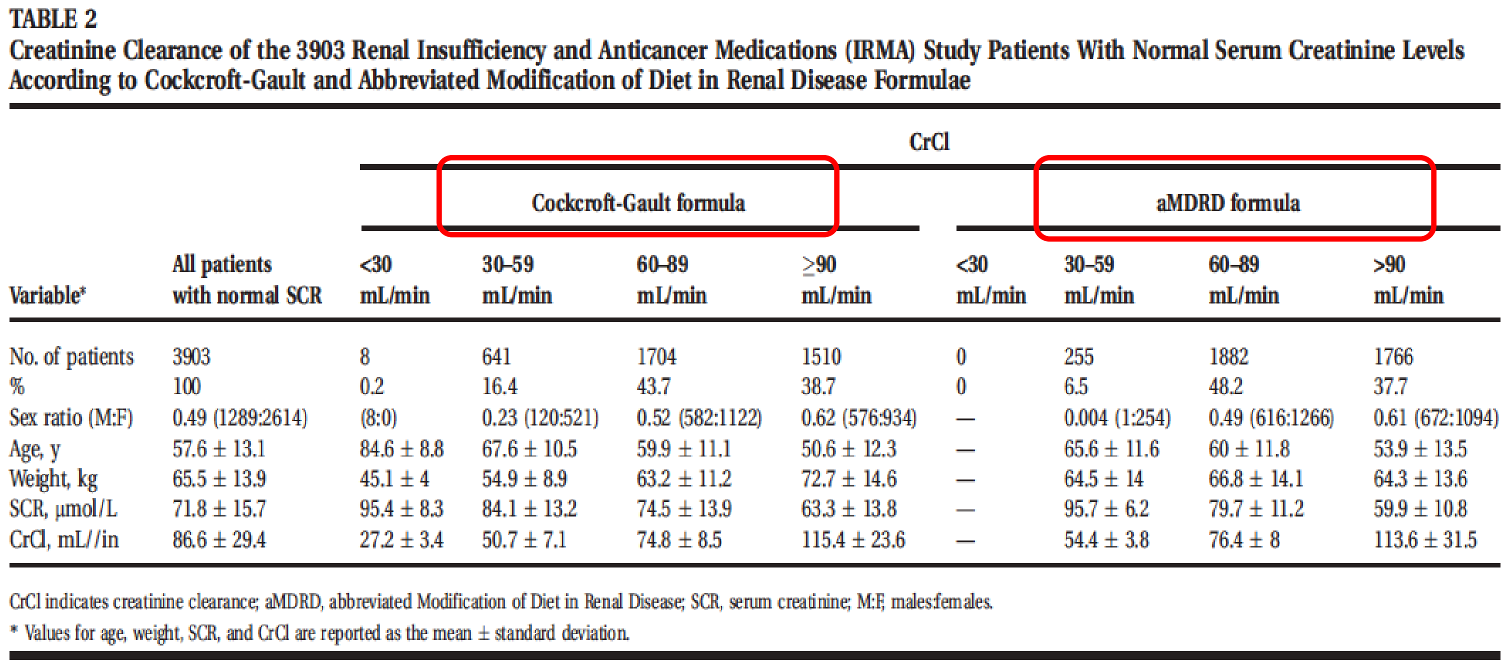


TABLE 2

Creatinine Clearance of the 3903 Renal Insufficiency and Anticancer Medications (IRMA) Study Patients With Normal Serum Creatinine Levels According to Cockcroft-Gault and Abbreviated Modification of Diet in Renal Disease Formulae

		CrCl							
		Cockcroft-Gault formula				aMDRD formula			
Variable*	All patients with normal SCR	<30 mL/min	30–59 mL/min	60–89 mL/min	≥90 mL/min	<30 mL/min	30–59 mL/min	60–89 mL/min	>90 mL/min
No. of patients	3903	8	641	1704	1510	0	255	1882	1766
%	100	0.2	16.4	43.7	38.7	0	6.5	48.2	37.7
Sex ratio (M:F)	0.49 (1289:2614)	(8:0)	0.23 (120:521)	0.52 (582:1122)	0.62 (576:934)	—	0.004 (1:254)	0.49 (616:1266)	0.61 (672:1094)
Age, y	57.6 ± 13.1	84.6 ± 8.8	67.6 ± 10.5	59.9 ± 11.1	50.6 ± 12.3	—	65.6 ± 11.6	60 ± 11.8	53.9 ± 13.5
Weight, kg	65.5 ± 13.9	45.1 ± 4	54.9 ± 8.9	63.2 ± 11.2	72.7 ± 14.6	—	64.5 ± 14	66.8 ± 14.1	64.3 ± 13.6
SCR, µmol/L	71.8 ± 15.7	95.4 ± 8.3	84.1 ± 13.2	74.5 ± 13.9	63.3 ± 13.8	—	95.7 ± 6.2	79.7 ± 11.2	59.9 ± 10.8
CrCl, mL//in	86.6 ± 29.4	27.2 ± 3.4	50.7 ± 7.1	74.8 ± 8.5	115.4 ± 23.6	—	54.4 ± 3.8	76.4 ± 8	113.6 ± 31.5

CrCl indicates creatinine clearance; aMDRD, abbreviated Modification of Diet in Renal Disease; SCR, serum creatinine; M:F, males:females.

* Values for age, weight, SCR, and CrCl are reported as the mean ± standard deviation.

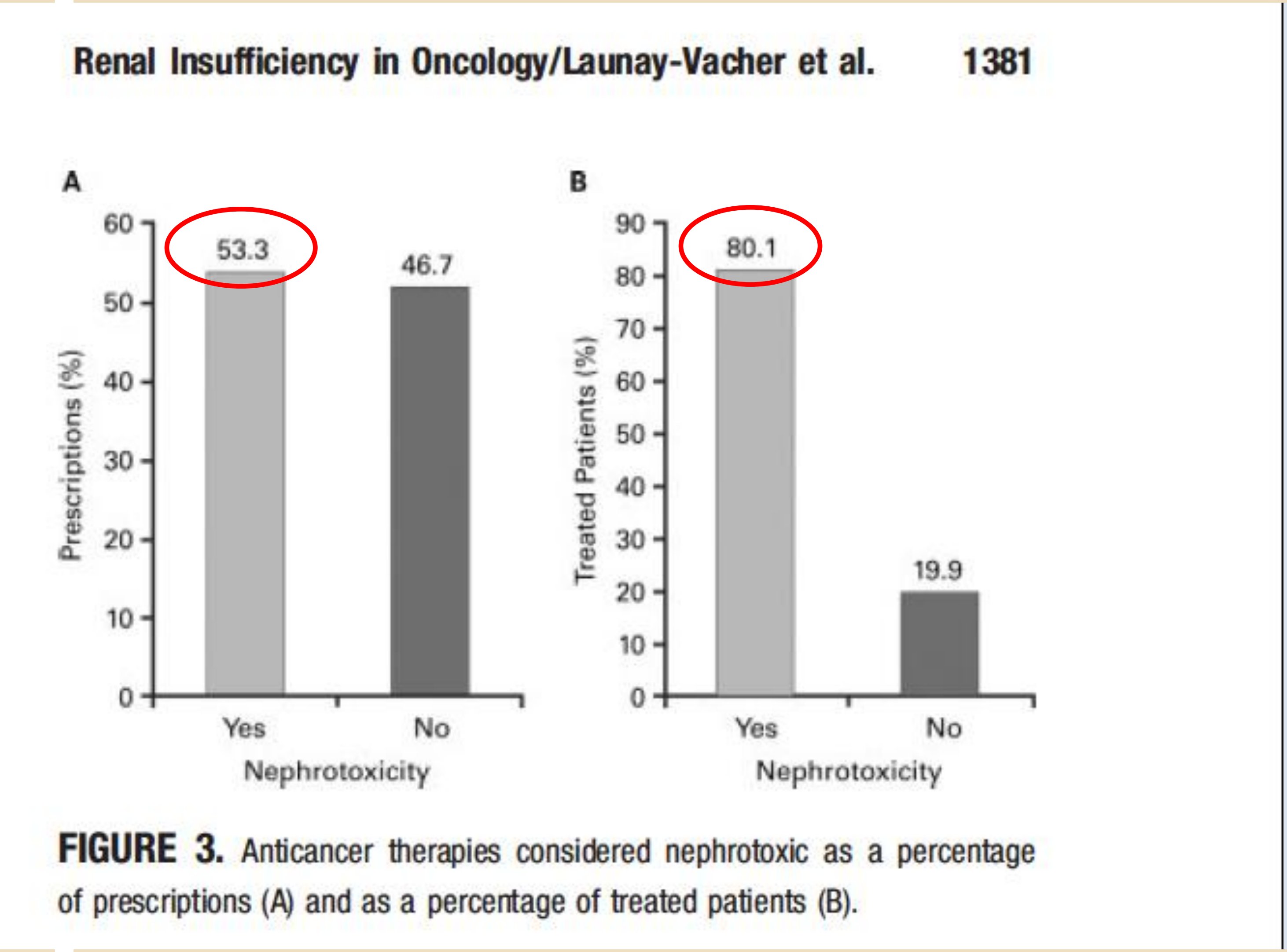


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FIGURE 3. Anticancer therapies considered nephrotoxic as a percentage of prescriptions (A) and as a percentage of treated patients (B).

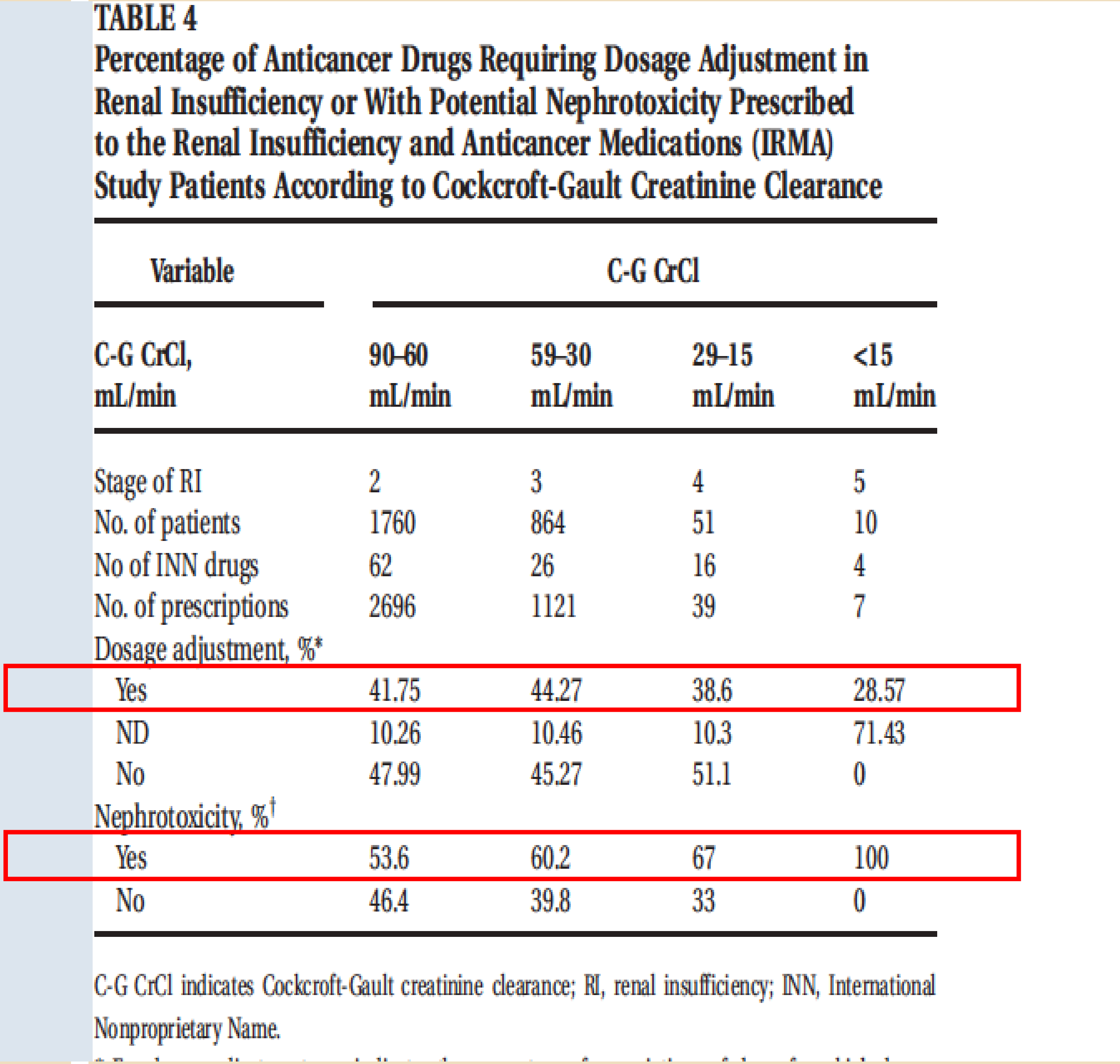
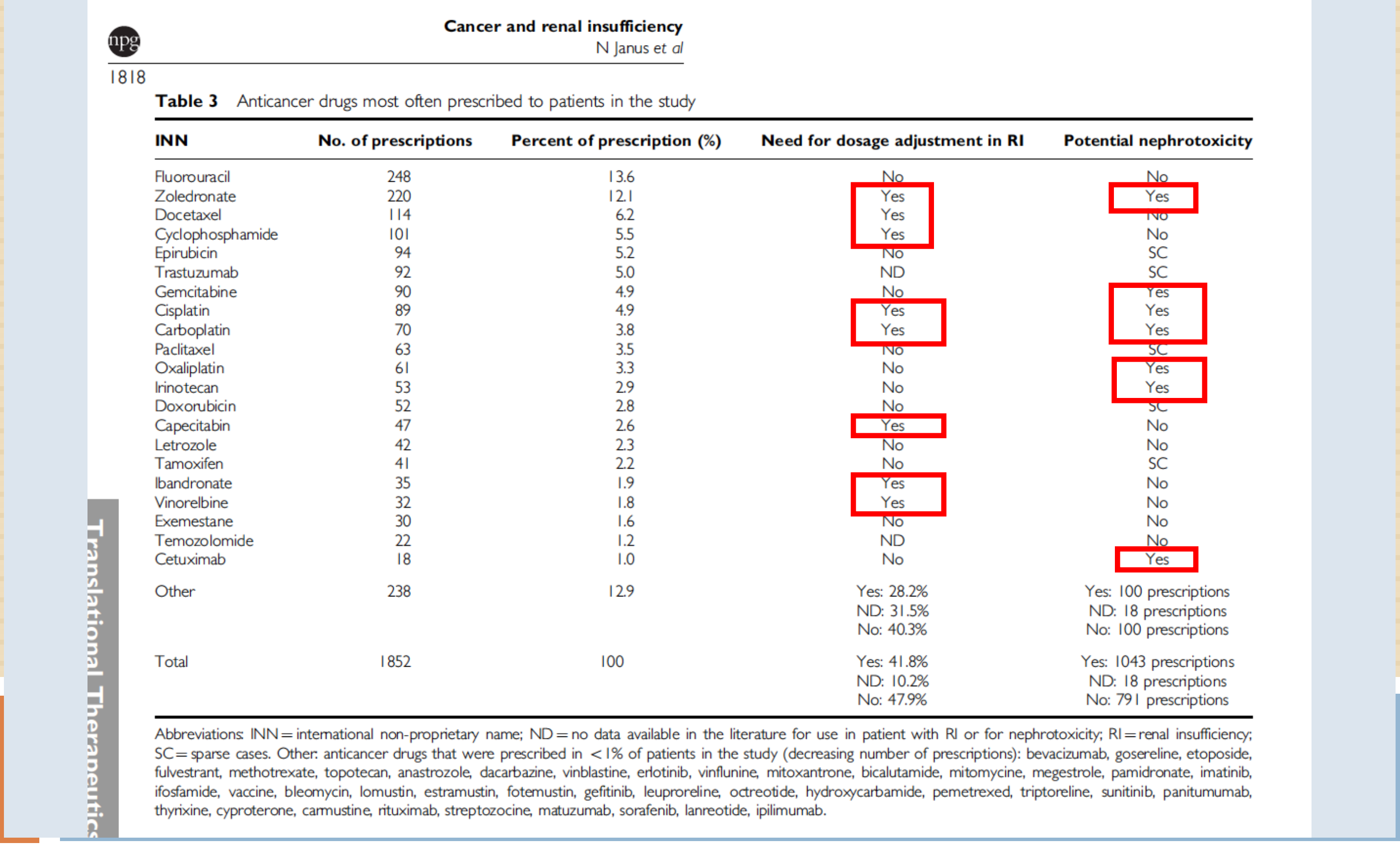


TABLE 4
Percentage of Anticancer Drugs Requiring Dosage Adjustment in Renal Insufficiency or With Potential Nephrotoxicity Prescribed to the Renal Insufficiency and Anticancer Medications (IRMA) Study Patients According to Cockcroft-Gault Creatinine Clearance

Variable	C-G CrCl			
C-G CrCl, mL/min	90–60 mL/min	59–30 mL/min	29–15 mL/min	<15 mL/min
Stage of RI	2	3	4	5
No. of patients	1760	864	51	10
No of INN drugs	62	26	16	4
No. of prescriptions	2696	1121	39	7
Dosage adjustment, %*				
Yes	41.75	44.27	38.6	28.57
ND	10.26	10.46	10.3	71.43
No	47.99	45.27	51.1	0
Nephrotoxicity, %†				
Yes	53.6	60.2	67	100
No	46.4	39.8	33	0

C-G CrCl indicates Cockcroft-Gault creatinine clearance; RI, renal insufficiency; INN, International Nonproprietary Name.

CHT e renal insufficiency Janus Annals of Oncology Vol 21; 71 395-1400, 2010



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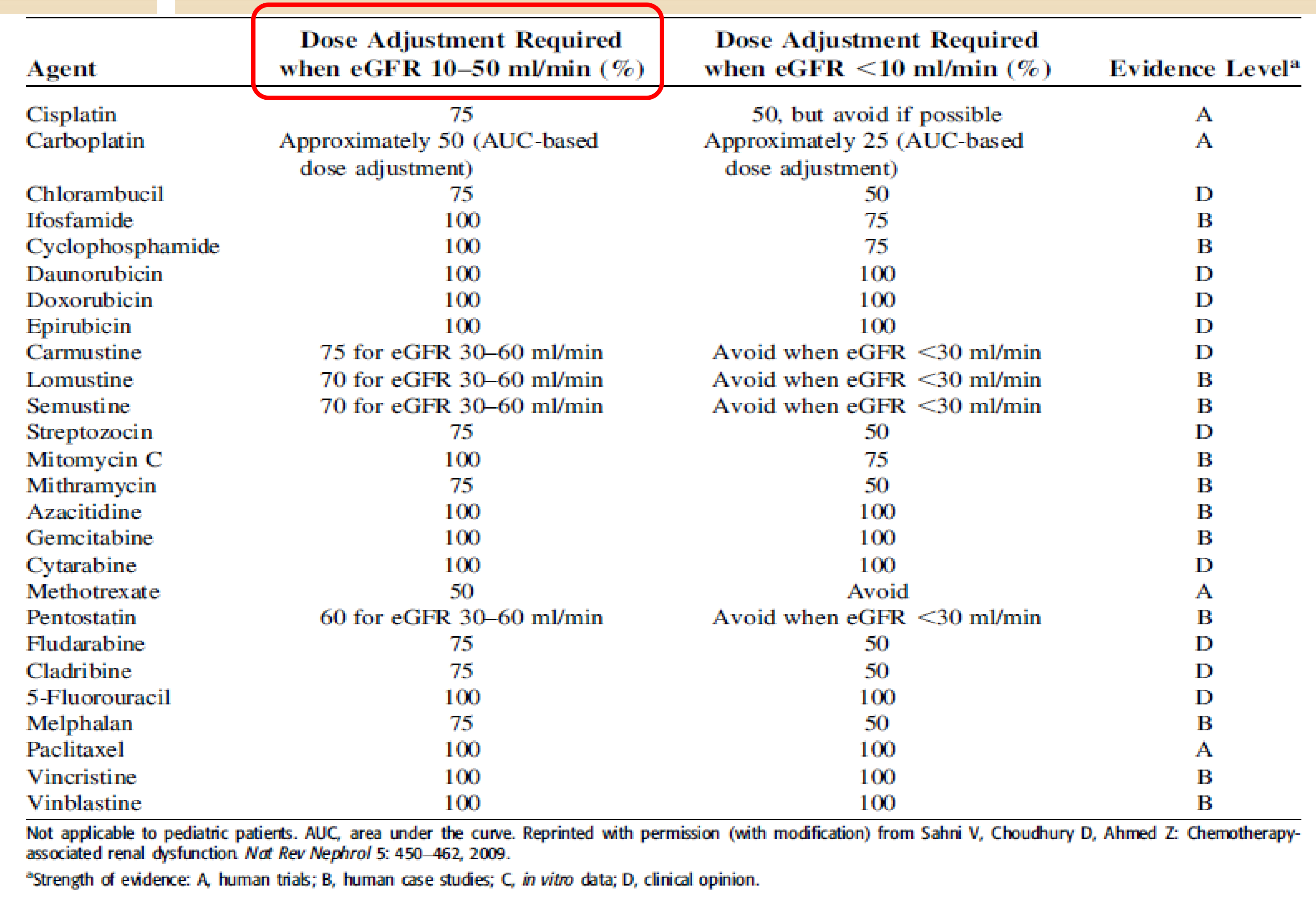
Translational Therapeutics

Table 3 Anticancer drugs most often prescribed to patients in the study

INN	No. of prescriptions	Percent of prescription (%)	Need for dosage adjustment in RI	Potential nephrotoxicity
Fluorouracil	248	13.6	No	No
Zoledronate	220	12.1	Yes	Yes
Docetaxel	114	6.2	Yes	No
Cyclophosphamide	101	5.5	Yes	No
Epirubicin	94	5.2	No	SC
Trastuzumab	92	5.0	ND	SC
Gemcitabine	90	4.9	No	Yes
Cisplatin	89	4.9	Yes	Yes
Carboplatin	70	3.8	Yes	Yes
Paclitaxel	63	3.5	No	SC
Oxaliplatin	61	3.3	No	Yes
Irinotecan	53	2.9	No	Yes
Doxorubicin	52	2.8	No	SC
Capecitabin	47	2.6	Yes	No
Letrozole	42	2.3	No	No
Tamoxifen	41	2.2	No	SC
Ibandronate	35	1.9	Yes	No
Vinorelbine	32	1.8	Yes	No
Exemestane	30	1.6	No	No
Temozolomide	22	1.2	ND	No
Cetuximab	18	1.0	No	Yes
Other	238	12.9	Yes: 28.2% ND: 31.5% No: 40.3%	Yes: 100 prescriptions ND: 18 prescriptions No: 100 prescriptions
Total	1852	100	Yes: 41.8% ND: 10.2% No: 47.9%	Yes: 1043 prescriptions ND: 18 prescriptions No: 791 prescriptions

Abbreviations: INN = international non-proprietary name; ND = no data available in the literature for use in patient with RI or for nephrotoxicity; RI = renal insufficiency; SC = sparse cases. Other: anticancer drugs that were prescribed in <1% of patients in the study (decreasing number of prescriptions): bevacizumab, gosereline, etoposide, fulvestrant, methotrexate, topotecan, anastrozole, dacarbazine, vinblastine, erlotinib, vinflunine, mitoxantrone, bicalutamide, mitomycine, megestrole, pamidronate, imatinib, ifosfamide, vaccine, bleomycin, lomustin, estramustin, fotemustin, gefitinib, leuproreline, octreotide, hydroxycarbamide, pemetrexed, triptoreline, sunitinib, panitumumab, thyrixine, cyproterone, carmustine, rituximab, streptozocine, matuzumab, sorafenib, lanreotide, ipilimumab.

Chemotherapy dose adjustment in patients with CKD



Agent	Dose Adjustment Required when eGFR 10–50 ml/min (%)	Dose Adjustment Required when eGFR <10 ml/min (%)	Evidence Level[a]
Cisplatin	75	50, but avoid if possible	A
Carboplatin	Approximately 50 (AUC-based dose adjustment)	Approximately 25 (AUC-based dose adjustment)	A
Chlorambucil	75	50	D
Ifosfamide	100	75	B
Cyclophosphamide	100	75	B
Daunorubicin	100	100	D
Doxorubicin	100	100	D
Epirubicin	100	100	D
Carmustine	75 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	D
Lomustine	70 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	B
Semustine	70 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	B
Streptozocin	75	50	D
Mitomycin C	100	75	B
Mithramycin	75	50	B
Azacitidine	100	100	B
Gemcitabine	100	100	B
Cytarabine	100	100	D
Methotrexate	50	Avoid	A
Pentostatin	60 for eGFR 30–60 ml/min	Avoid when eGFR <30 ml/min	B
Fludarabine	75	50	D
Cladribine	75	50	D
5-Fluorouracil	100	100	D
Melphalan	75	50	B
Paclitaxel	100	100	A
Vincristine	100	100	B
Vinblastine	100	100	B

Not applicable to pediatric patients. AUC, area under the curve. Reprinted with permission (with modification) from Sahni V, Choudhury D, Ahmed Z: Chemotherapy-associated renal dysfunction. *Nat Rev Nephrol* 5: 450–462, 2009.

[a] Strength of evidence: A, human trials; B, human case studies; C, *in vitro* data; D, clinical opinion.

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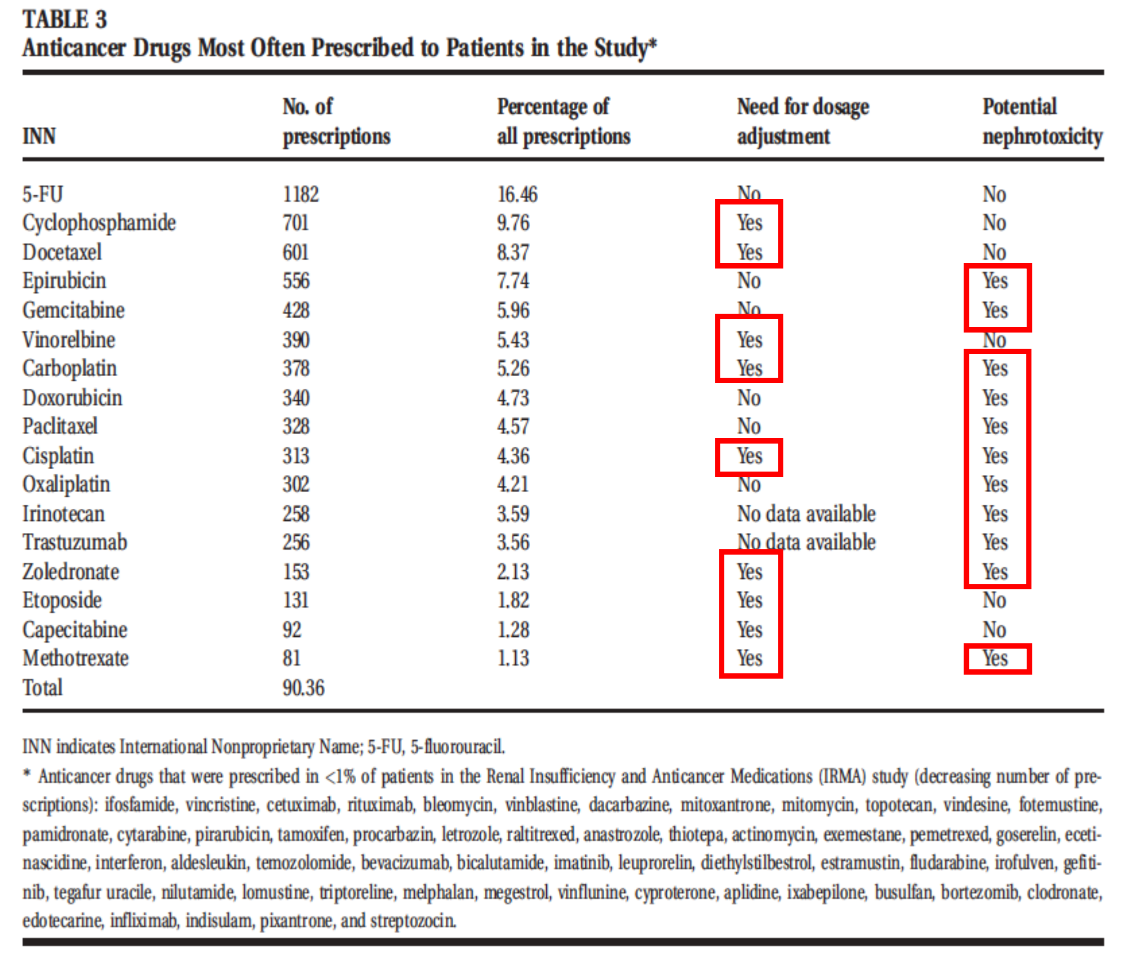

TABLE 3
Anticancer Drugs Most Often Prescribed to Patients in the Study*

INN	No. of prescriptions	Percentage of all prescriptions	Need for dosage adjustment	Potential nephrotoxicity
5-FU	1182	16.46	No	No
Cyclophosphamide	701	9.76	Yes	No
Docetaxel	601	8.37	Yes	No
Epirubicin	556	7.74	No	Yes
Gemcitabine	428	5.96	No	Yes
Vinorelbine	390	5.43	Yes	No
Carboplatin	378	5.26	Yes	Yes
Doxorubicin	340	4.73	No	Yes
Paclitaxel	328	4.57	No	Yes
Cisplatin	313	4.36	Yes	Yes
Oxaliplatin	302	4.21	No	Yes
Irinotecan	258	3.59	No data available	Yes
Trastuzumab	256	3.56	No data available	Yes
Zoledronate	153	2.13	Yes	Yes
Etoposide	131	1.82	Yes	No
Capecitabine	92	1.28	Yes	No
Methotrexate	81	1.13	Yes	Yes
Total	90.36			

INN indicates International Nonproprietary Name; 5-FU, 5-fluorouracil.

* Anticancer drugs that were prescribed in <1% of patients in the Renal Insufficiency and Anticancer Medications (IRMA) study (decreasing number of prescriptions): ifosfamide, vincristine, cetuximab, rituximab, bleomycin, vinblastine, dacarbazine, mitoxantrone, mitomycin, topotecan, vindesine, fotemustine, pamidronate, cytarabine, pirarubicin, tamoxifen, procarbazin, letrozole, raltitrexed, anastrozole, thiotepa, actinomycin, exemestane, pemetrexed, goserelin, ecteinascidine, interferon, aldesleukin, temozolomide, bevacizumab, bicalutamide, imatinib, leuprorelin, diethylstilbestrol, estramustin, fludarabine, irofulven, gefitinib, tegafur uracile, nilutamide, lomustine, triptoreline, melphalan, megestrol, vinflunine, cyproterone, aplidine, ixabepilone, busulfan, bortezomib, clodronate, edotecarine, infliximab, indisulam, pixantrone, and streptozocin.

BIRMA study Janus BJC 103: 1815-1821 , 2010

Conclusioni

- **Conoscere da parte dell'oncologo medico la fisiopatologia del danno renale** da chemioterapici lo rende più consapevole dei rischi e più esperto nella gestione della complicanze renali
- **La collaborazione strutturata col nefrologo** porta ad un riconoscimento più precoce delle patologie renali in corso di trattamenti antiblastici e una più adeguata prevenzione di danni permanenti
- Quando si rende **necessario in corso di trattamento antitumorale ricalibrare le dosi** per non aggravare problematiche renali pre-esistenti o di nuova insorgenza , dal confronto tra oncologo e nefrologo ne possono derivare decisioni ragionate e basate sull'evidenza