Imunoterapija: treba li se nefrolog bojati?

Zajednički simpozij Hrvatskog društva za internističku onkologiju i Hrvatskog društva za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

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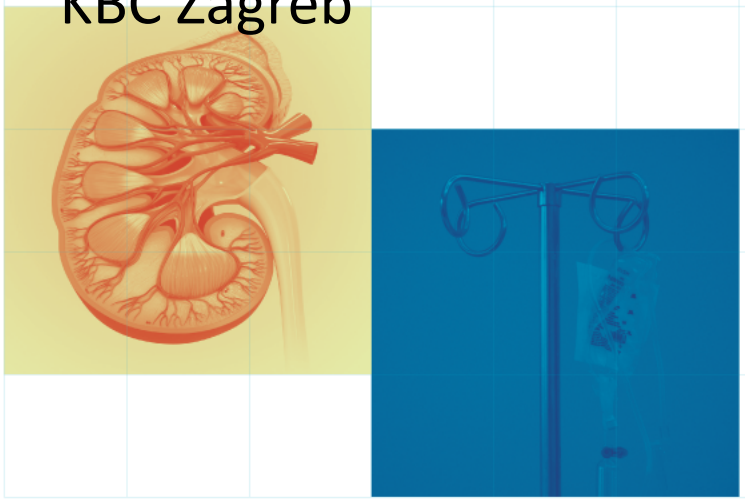


8.2.2020.

Hrvatski liječnički zbor, Zagreb

HDIO

Hrvatsko društvo za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora

Uloga imunološkog sustava u pojavi raka

- 1957 - prvi eksperimentalni dokazi o ulozi imunološkog sustava u razvoju karcinoma
- temelji se na istraživanja na eksperimentalnim modelima s transplantibilnim tumorima i zapažanjima spontane regresije tumora u čovjeka
- hipoteza o postojanju sustava koji prepoznaje i uništava tumore nastale u tkivima
- teorija o imunološkom sustavu koji razlikuje “vlastito” od “stranog”

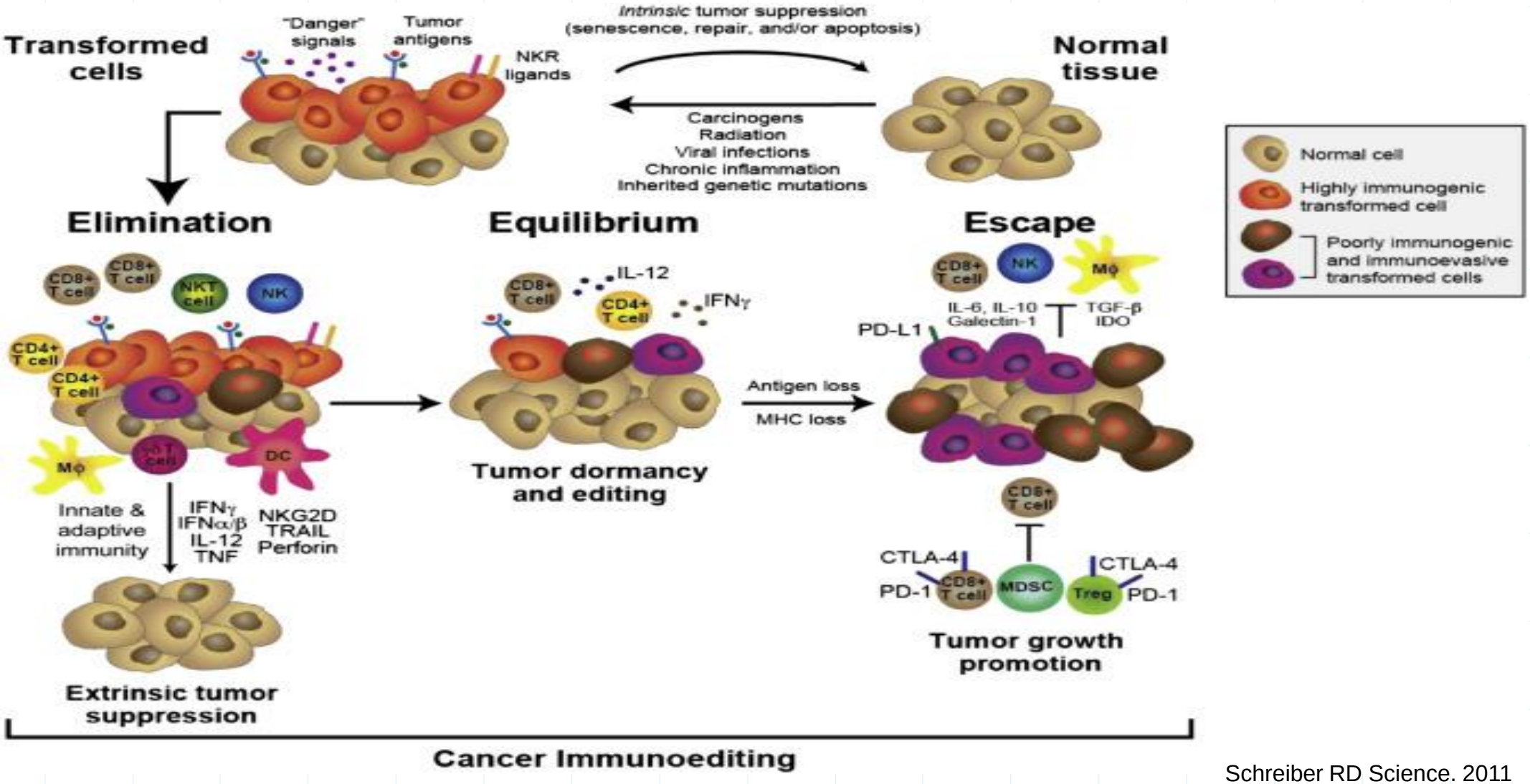
Prehn RTJ Natl Cancer Inst. 1957

Olivera JF J Immunol. 2018

Imunoeditiranje

- mehanizam kojim imunološki sustav sprječava, kontrolira i oblikuje tumor
- 3 faze:
- 1.eliminacijska faza – cilj je uništenje tumora u nastajanju
- 2. stanje ekvilibrija- tumor se drži u stanju funkcionalne dormancije
- 3. faza bijega tumorskih stanica

Dunn GP Nat Immunol. 2002



Schreiber RD Science. 2011

- imunološki sustav posjeduje složene mehanizme kojima održava homoeostazu
- nekontrolirana aktivacija na patogene ili vlastite antigene bi dovela do oštećenja tkiva i autoimunih bolesti
- ta se homeostaza održava ravnotežom između kostimulacijskih i inhibicijskih signala – imunosne nadzorne točke (immune chekpoints)
- stimulacijom pojedinih nadzornih točaka tumori izbjegavaju imunološki reakciju
- CTLA-4 i PD1

Pardoll DM Nat Rev Cancer. 2012

INHIBICIJOM CTLA-4 I PD-1 STIMULIRAMO IMUNOLOŠKI ODGOVOR

PD-1 potiskuje funkciju T stanica vezanjem za PD-L1 and PD-L2

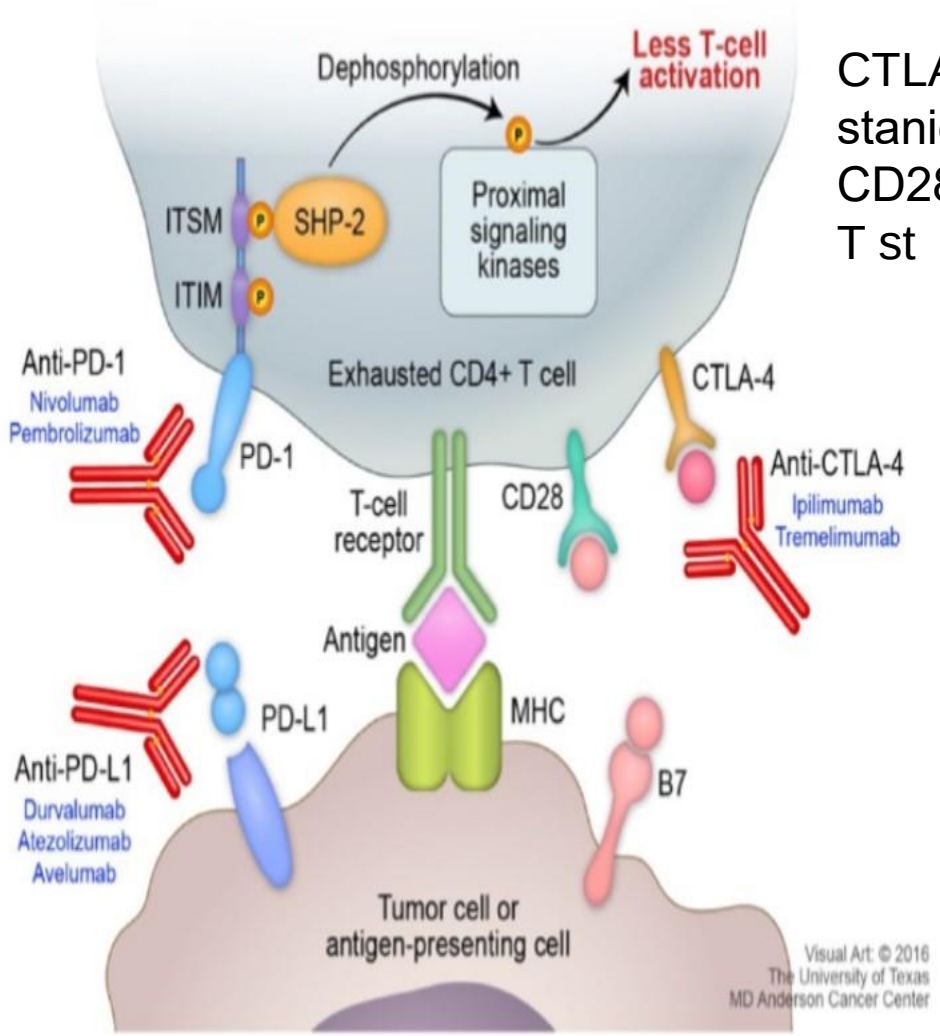


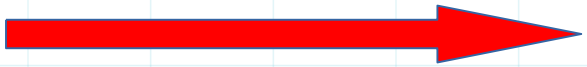
Figure 1. PD-1/PD-L1 pathway and immunotherapy targets.
ITSM, immunoreceptor tyrosine-based switch motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; PD-1, programmed-death 1; PD-L1, programmed death-ligand 1; CD28, cluster of differentiation 28; MHC, major histocompatibility complex; SHP-2, Src homology 2 (SH2) domain containing non-transmembrane PTP; B7, B7 protein; CTLA-4, cytotoxic T-lymphocyte

CTLA-4 sprječava aktivaciju T stanica vežući se za B7 istiskujući CD28 čime se inhibira kostimulacija T st

Schvartsman G Ther Adv Med Oncol .2016

Razvoj imunoterapije

- IL-2
- IFN alfa-2b
- melanom
- rak bubrega

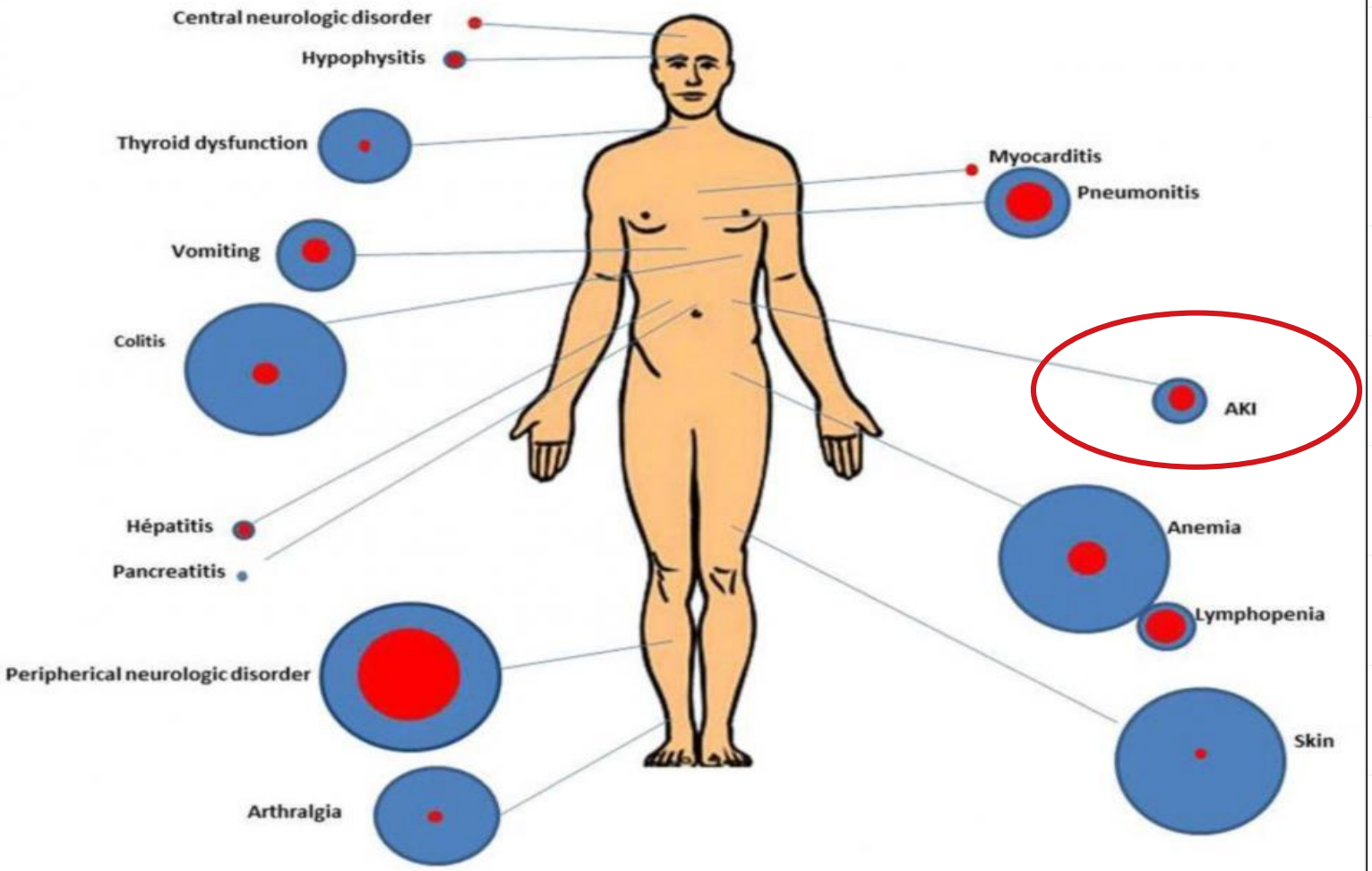


- “checkpoint” inhibitori
- PD-1/PD-L1 inhibitori
- CTLA-4 inhibitori
- melanom, rak bubrega, pluća, jajnika, urotelni karcinom, tumori glave i vrata, želuca, jetre, HL, “Merkel cell” tumor, MSI-H/dMMR tumori

Nuspojave imunoterapije

- razlikuju se od nuspojava “klasične” kemoterapije
- podaci o učestalosti nuspojava imunoterapije se još uvijek prikupljaju
- vrijeme pojavljivanja je teško predvidivo- mogu se javiti i nakon prekida liječenja
- patofiziologija nije razjašnjena- objašnjava se pojačanom aktivacijom T stanica te vezanjem protutijela na molekule eksprimirane u zdravim tkivima (ekspresija CTLA u hipofizi)
- priroda nuspojava otežava prepoznavanje i prijavljivanje – podaci u literaturi vjerojatno podcjenjuju njihovu učestalost
- zahvaćaju mnoge organske sustave
- rane i kasne

Kumar V Front Pharmacol 2017



Credit: Ann Intensive Care. Feb. 2019

Veličina kruga opisuje incidenciju nuspojave, plava boja označava toksičnost bilo kojeg stupnja, a crvena toksičnost visokog stupnja

Akutno bubrežno oštećenje

- prevalencija – 2% za monoterapiju, do 4,9 % za kombinaciju
- G III/IV -0,6 % (1,7%)
- ~3 mj. od početka terapije (3 tj- 8 mj)
- akutni tubulointertsicijski nefritis - najčešće
- azotemija, smanjena diureza

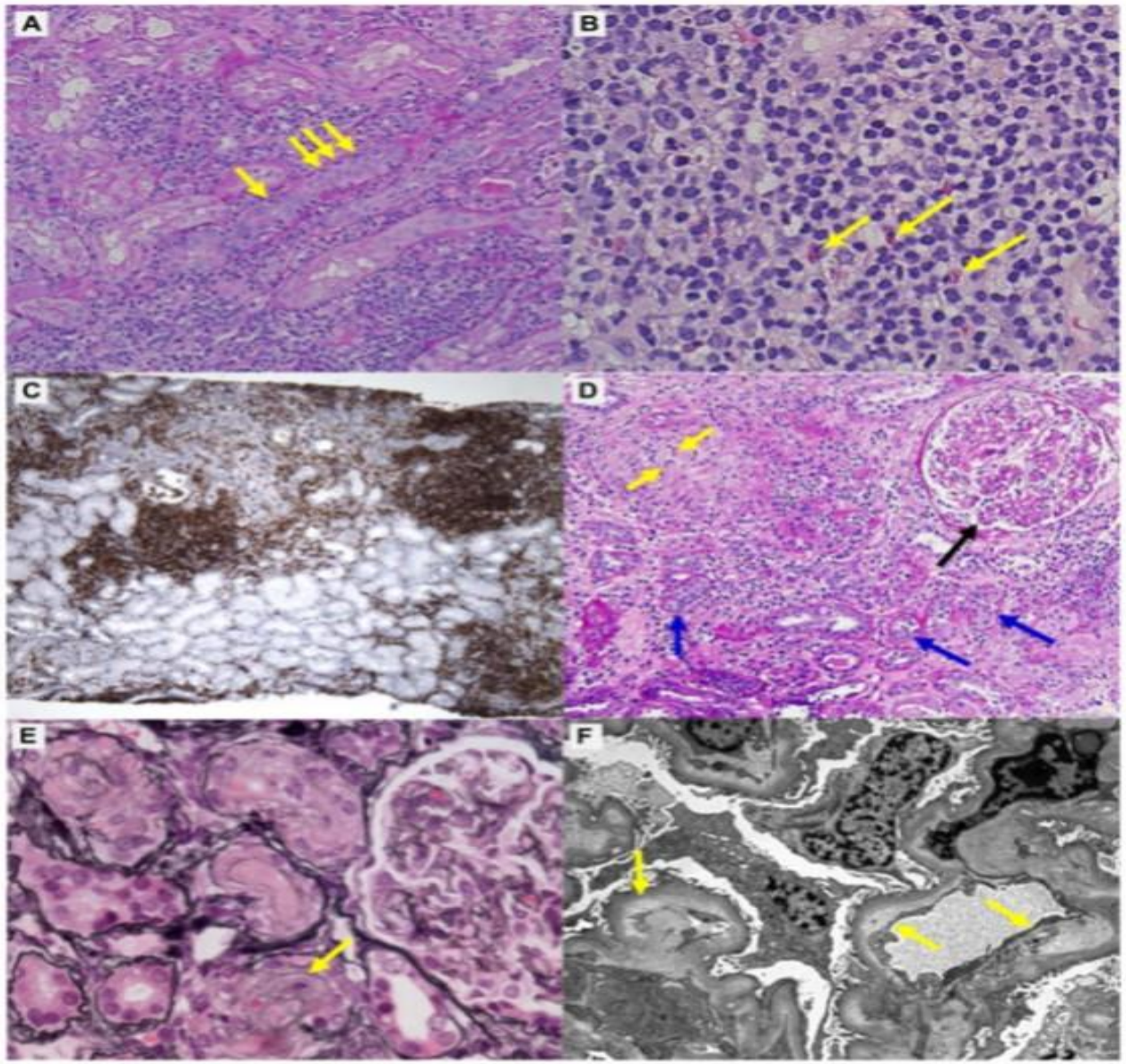
Cortazar FB Kidney Int. 2016

CTCAE v4.0

Renal and urinary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					

- Cortazar et al.- najveća objavljena serija bolesnika
- melanom pretežno, th: ipilimumab, nivolumab, nivo+ ipi, pembrolizumab
- piurija, proteinurija, hipertenzija, porast kreatinina
- 7 bolesnika je imalo ekstrarenalnu iRAE
- 13 bolesnika s bubrežnim oštećenjem
- biopsija bubrega :
- akutni tubulointersticijski nefritis 12 bolesnika
- trombotička mikorangiopatija 1 bolesnik

Cortazar FB Kidney Int. 2016



A-C akutni tubulointersticijski nefritis
D granulomatozni tubulointersticijski nefritis
E-F akutna trombotička mikorangiopatija

Cortazar FB Kidney Int. 2016

- razlikovanje AIN uzrokovanog imunoterapijom od AIN druge etiologije - različito liječnje
- serija bolesnika liječenih imunoterapijom kojima je učinjena biopsija bubrega zbog akutnog oštećenja
- 15 uzoraka (9 AIN , 6 ATN); kontrola 9 uzoraka AIN koji nisu primali imunoterapiju i 9 s lupus nefritisom
- različiti imunohistokemijski uzorak PD-1/PD-L1

C Cassol Kidney International Reports 2019

Table 5. Immunohistochemistry findings in kidney biopsy specimens

			PD-1		PDL-1			
			Inflammatory cells		Inflammatory cells		Tubular epithelial cells	
Cases			Intensity/%	Pattern	Intensity/%	Pattern	Intensity/%	Pattern
PD-1 inhibitor therapy	Interstitial nephritis (group 1)	1	Strong/20	Diffuse	Strong/30	Diffuse	Strong/50	Focal
		2	Weak/5	Focal	Strong/5	Focal	Strong/15	Focal
		3	Weak/15	Diffuse	Weak/10	Focal	Weak/10	Focal
		4	Weak/10	Focal	Strong/10	Focal	Strong/15	Focal
		5	Weak /10	Diffuse	Weak/5	Focal	Strong/5	Focal
		6	Weak/5	Focal	Strong/5	Focal	Strong/5	Focal
		7	Weak/1	Focal	Weak/1	Focal	Weak/3	Focal
		8	Weak/10	Diffuse	Strong/20	Focal	Strong/40	Focal
		9	Strong/10	Diffuse	Strong/5	Focal	Strong/5	Focal
	No interstitial nephritis (group 2)	10	Weak/2	Focal	Negative	Negative	Negative	Negative
		11	Weak/2	Focal	Negative	Negative	Negative	Negative
		12	Weak/2	Focal	Negative	Negative	Negative	Negative
		13	Weak/2	Focal	Weak/2	Focal	Negative	Negative
		14	Weak/2	Focal	Negative	Negative	Negative	Negative
		15	Weak/5	Focal	Weak/1	Focal	Negative	Negative
No history of PD-1 inhibitor therapy	Interstitial nephritis	16	Weak/10	Focal	Negative	Negative	Negative	Negative
		17	Weak/2	Focal	Negative	Negative	Negative	Negative
		18	Weak/2	Focal	Negative	Negative	Negative	Negative
		19	Weak/2	Focal	Negative	Negative	Negative	Negative
		20	Strong/20	Focal	Negative	Negative	Negative	Negative
		21	Weak/5	Focal	Weak/1	Focal	Negative	Negative
		22	Weak/10	Diffuse	Negative	Negative	Negative	Negative
		23	Weak/5	Focal	Weak/1	Focal	Negative	Negative
		24	Weak/5	Focal	Negative	Negative	Negative	Negative
	Lupus nephritis with active interstitial inflammation	25	Moderate/10	Diffuse	Negative	Negative	Negative	Negative
		26	Weak/1	Focal	Negative	Negative	Negative	Negative
		27	Weak/1	Focal	Negative	Negative	Negative	Negative
		28	Strong/5	Focal	Negative	Negative	Negative	Negative
		29	Weak/<1	Focal	Weak/1	Focal	Negative	Negative
		30	Moderate/2	Focal	Negative	Negative	Negative	Negative
		31	Weak/2	Focal	Negative	Negative	Negative	Negative
		32	Weak/5	Focal	Negative	Negative	Negative	Negative
		33	Negative	Negative	Negative	Negative	Negative	Negative
	Baseline	34	Negative	Negative	Negative	Negative	Negative	Negative
		35	Weak/<1 in PTC	Very focal	Negative	Negative	Negative	Negative
		36	Negative	Negative	Negative	Negative	Negative	Negative
		37	Negative	Negative	Negative	Negative	Negative	Negative
		38	Negative	Negative	Negative	Negative	Weak/<1	Very focal

PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PTC, peritubular capillaries.

Stanice tubula su bile pozitivne na PD-L1 samo u bolesnika liječenjih PD-1 inhibitorima koji su razvili AIN

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Posebne skupine bolesnika

- imunoterapija se može primjenjivati u bolesnika s preegzistentnim oštećenjem bubrežne funkcije i na dijalizi
- transplantirani bolesnici nisu bili uključivani u studije s imunoterapijom- postoje objavljeni radovi o primjeni ipilimumaba u bolesnika s transplantiranom jetrom i bubregom
- objavljeni su slučajevi odbacivanja bubrega u bolesnika liječenih imunoterapijom (PD-1 inhibitori)
- potreban je individualizirani pristup u transplantiranih bolesnika

Kittai AS J Immunother. 2017

Principi liječenja iRAE

- preporuča se multidisciplinarni pristup i subspecijalistička konzultacija u zbrinjavanju nuspojava
- 1. Prepoznavanje i određivanje stupnja nuspojave
- 2. Imunosupresija
- GLUKOKORTIKOIDI- dovoljno duga primjena i postupno ukidanje (ne smanjuje se antitumorski učinak imunoterapije)
- ostali imunomodulatori (anti-TNF-a, MMF, IVIG , itd.)
- 3. Individualizirana modifikacija primjene imunoterapije

Postupak kod sumnje na akutno bubrežno ostećenje uzrokovano imunoterapijom

- porast kreatinina ⟶ isključiti/ zamijeniti potencijalne nefrotoksične lijekove
- prilagoditi dozu lijekova ovisno o stupnju oštećenja bubrežne funkcije
- isključiti ostale uzroke bubrežne insuficijencije- prerenalne i postrenalne (dehidracija zbog kolitisa, primjena kontratsa, infekcija, primjena diuretika, bolesti srca i sl.)
- nuspojave G ≥ 2- konzultirati nefrologa, razmotriti biopsiju

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
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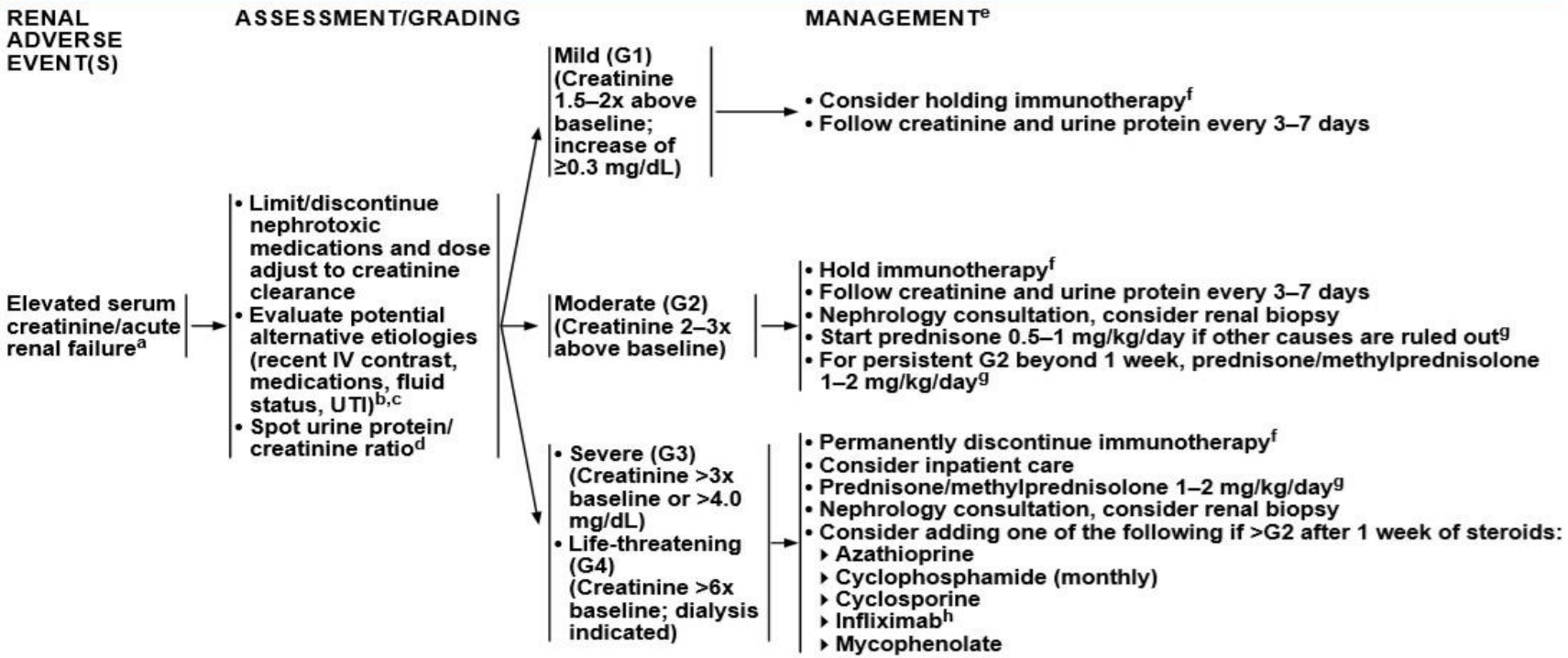


[a] Azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, and urine output change.
[b] General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDs and PPIs, and consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
[c] Distinguish cell infiltrate (consider vasculitis) vs. immune-complex–mediated renal injury.
[d] For proteinuria >3 g/24-hour, check ANA, RF, ANCA, anti-dsDNA, and serum C3, C4, and CH50.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] An FDA-approved biosimilar is an appropriate substitute for infliximab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ICI_RENAL-1

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

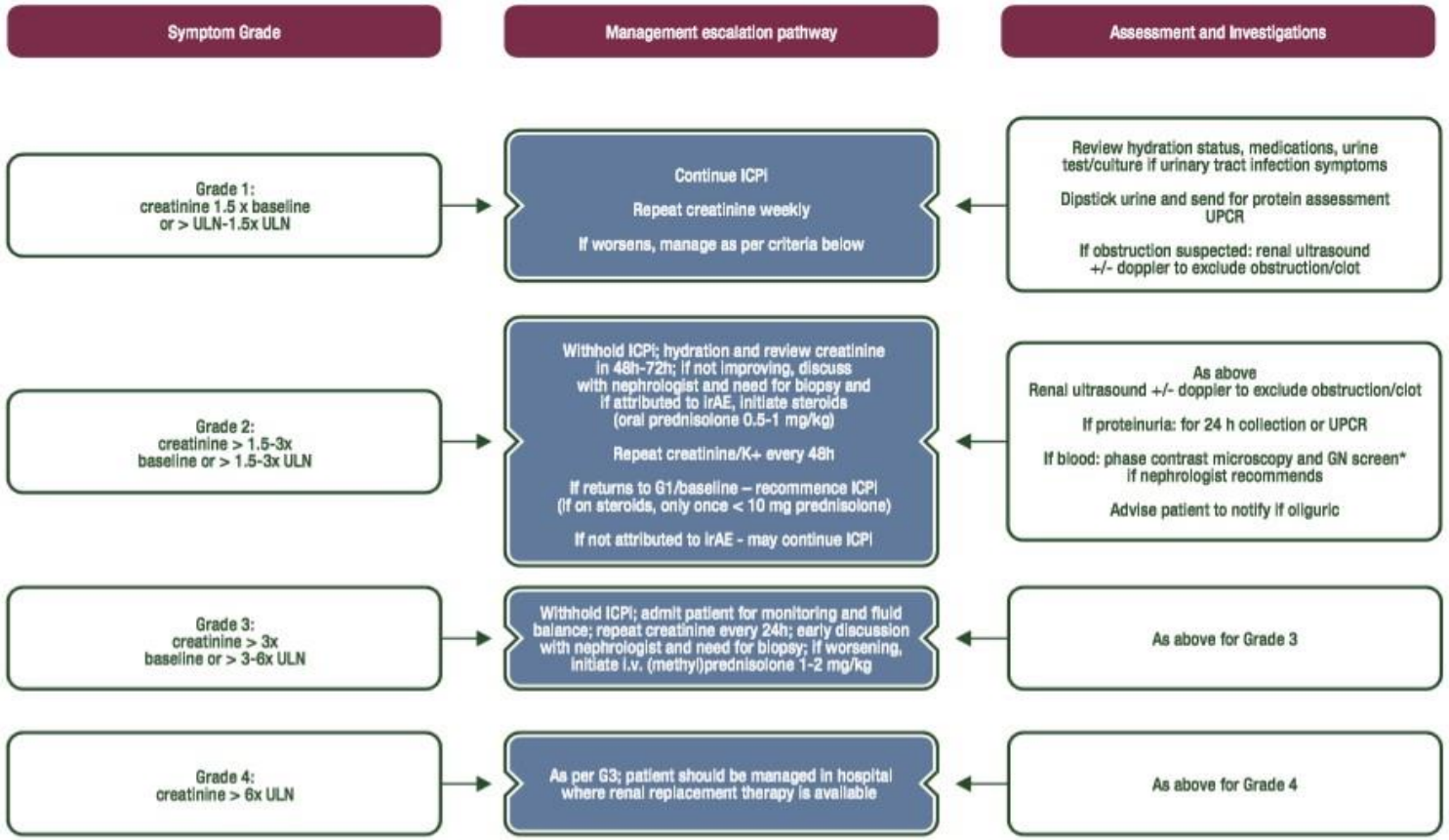
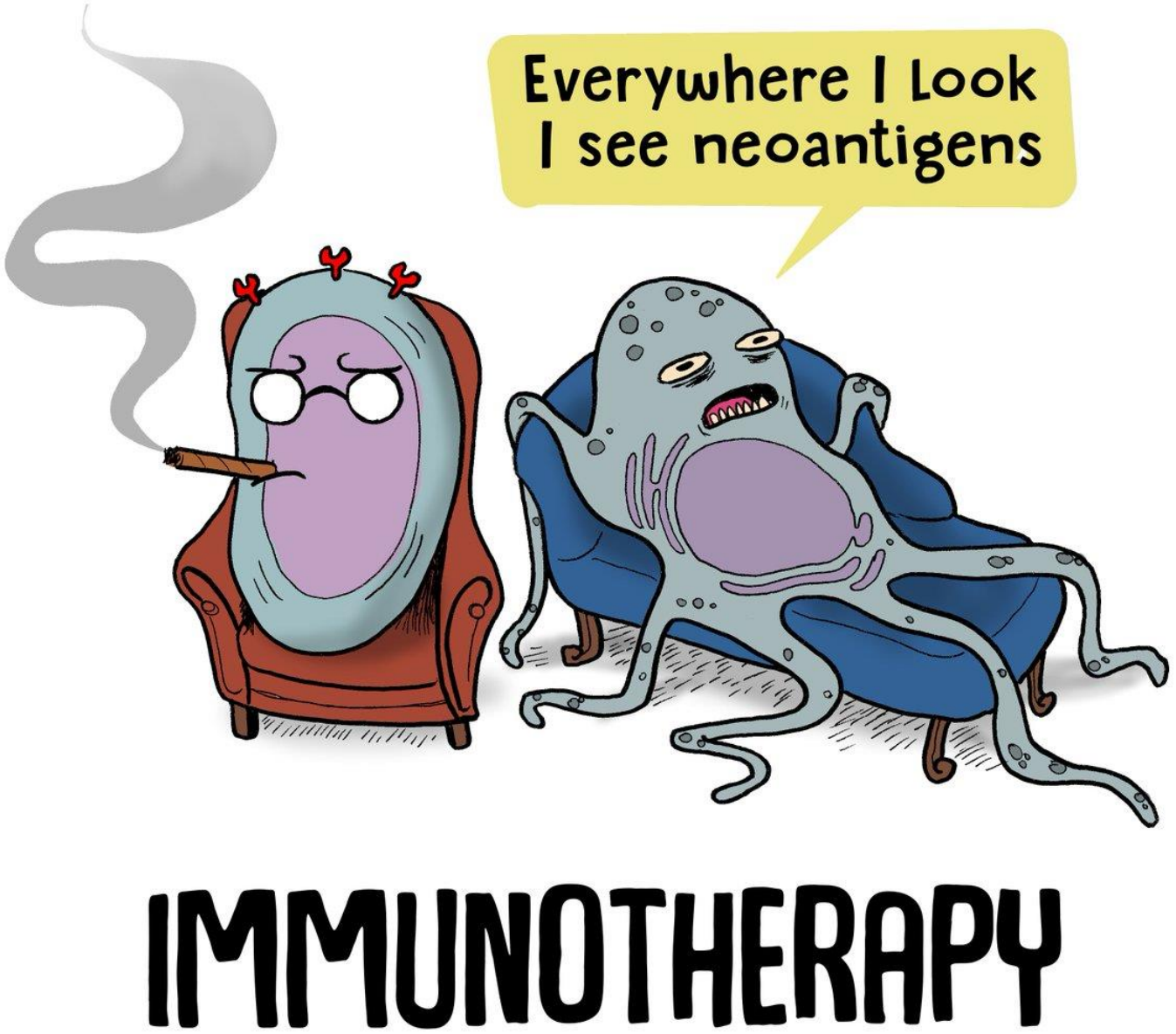


Figure 14. ICPi-related toxicity: management of nephretis.
Renal injury occurs in around 1%–4% of patients treated with ICPi, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate [80]. Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN. Confounding diagnoses include dehydration, recent i.v. contrast, urinary tract infection, medications, hypotension, or hypertension. Early consideration for renal biopsy is helpful which may negate the need for steroids and determine whether renal deterioration is related to ICPis or other pathology. Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy. Steroid wean: begin to wean once creatinine G1; G2 severity episode—wean steroids over 2–4 weeks; G3/4 episode—wean over ≥ 4 weeks. If on steroids for > 4 weeks—PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia. *GN screen: ANA, complement C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis.
ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; GBM; glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; i.v., intravenous; K, potassium; PJP, Pneumocystis jiroveci pneumonia; ULN, upper limit of normal; UPCR, urine protein to creatinine ratio.

Mora li se nefrolog bojati imunoterapije?

- NE,ali treba biti oprezan:
- mehanizmi nastanka akutnog bubrežnog oštećenja i njihova učestalost nisu dovoljno poznati
- na vrijeme prepoznati nuspojavu -vrijeme početka nuspojave nepredvidivo
- isključiti druge potencijalne uzroke pogoršanja renalne funkcije
- na vrijeme započeti liječenje i dovoljno dugo liječiti

HVALA NA PAŽNJI !



Hrvatsko društvo za nefrologiju,
dijalizu i transplantaciju
Hrvatskog liječničkog zbora