# The scope and impact of kidney disorders in cancer

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# Exploring the Present and Imagining the Future Landscape of Onconephrology

Abinet M. Aklilu [1,2] and Anushree C. Shirali [1]

From its beginnings in 2010 , the field of onconephrology has now expanded to become a subspecialty within nephrology.
A specialized field **bridging the world** of **oncology** and **nephrology** became necessary for multiple reasons.
Key among these reasons:

(1) **off-target acute and chronic effects** of established and **novel anticancer therapeutics on kidney function**
(2) **pharmacokinetics** of **anticancer drugs cleared** or **metabolized by the kidney**
(3) **direct acute effects of cancer on kidney function**
(4) **longitudinal care of kidney disease in long-term survivors** of cancer.

Kidney360 5: 1377–1379, 2024.

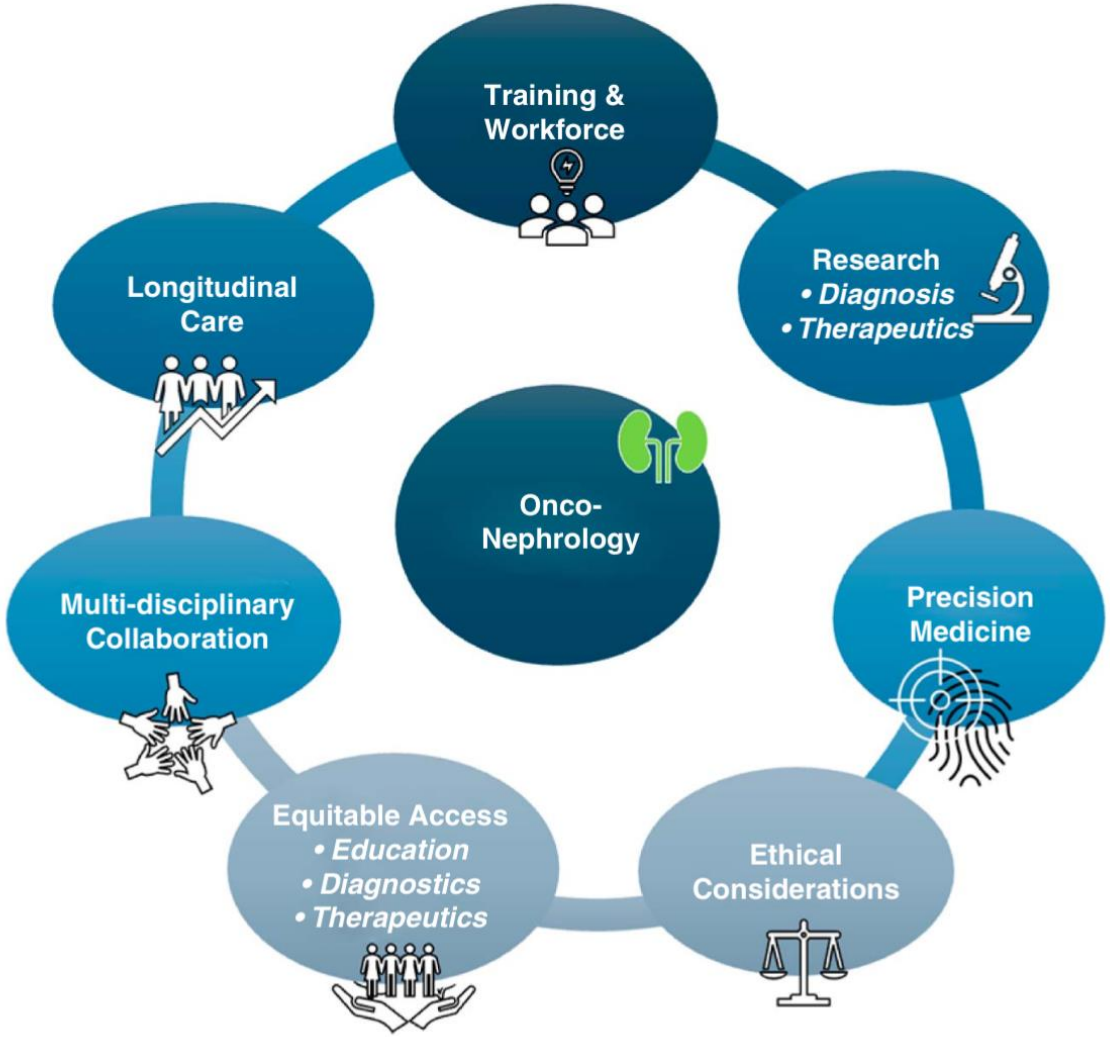


Figure 1. Onconephrology: a new paradigm.

# Impact of Cancer on Kidneys

- Chemotherapy and radiation
- TLS
- Metastasis
- Paraneoplastic Syndromes
- Obstruction

# Impact of Kidney Health on Cancer

- Kidney function and treatment
- Increased risk of cancer
- Uremic toxins

# Onconephrology: The Intersections Between the Kidney and Cancer

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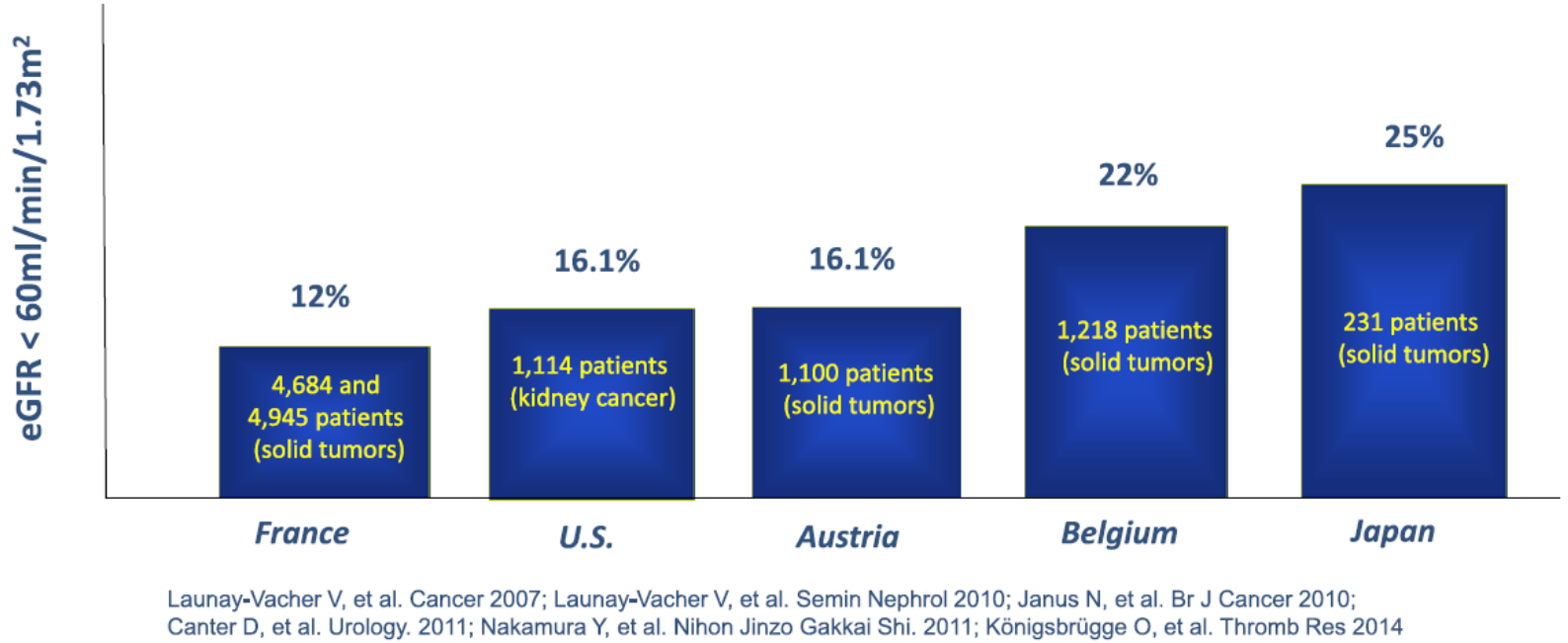
CA CANCER J CLIN 2021;71:47–77




Launay-Vacher V, et al. Cancer 2007; Launay-Vacher V, et al. Semin Nephrol 2010; Janus N, et al. Br J Cancer 2010; Canter D, et al. Urology. 2011; Nakamura Y, et al. Nihon Jinzo Gakkai Shi. 2011; Königsbrügge O, et al. Thromb Res 2014

FIGURE 1. The Prevalence of Chronic Kidney Disease (Estimated Glomerular Filtration Rate [eGFR] <60 mL/Minute/1.73 $m^2$) in Various Cohorts of Patients With Cancer Across the World.[1-9] Percentages listed are those from patients with cancer who had an eGFR <60 mL/minute/1.73 $m^2$. Adapted from: Launay-Vacher et al, 2007[1]; Launay-Vacher, 2010[2]; Janus, 2010[5]; Canter et al, 2011[10]; Nakamura, 2011[11]; and Konigsbrugge et al, 2014.[12]

CA CANCER J CLIN 2021;71:47–77

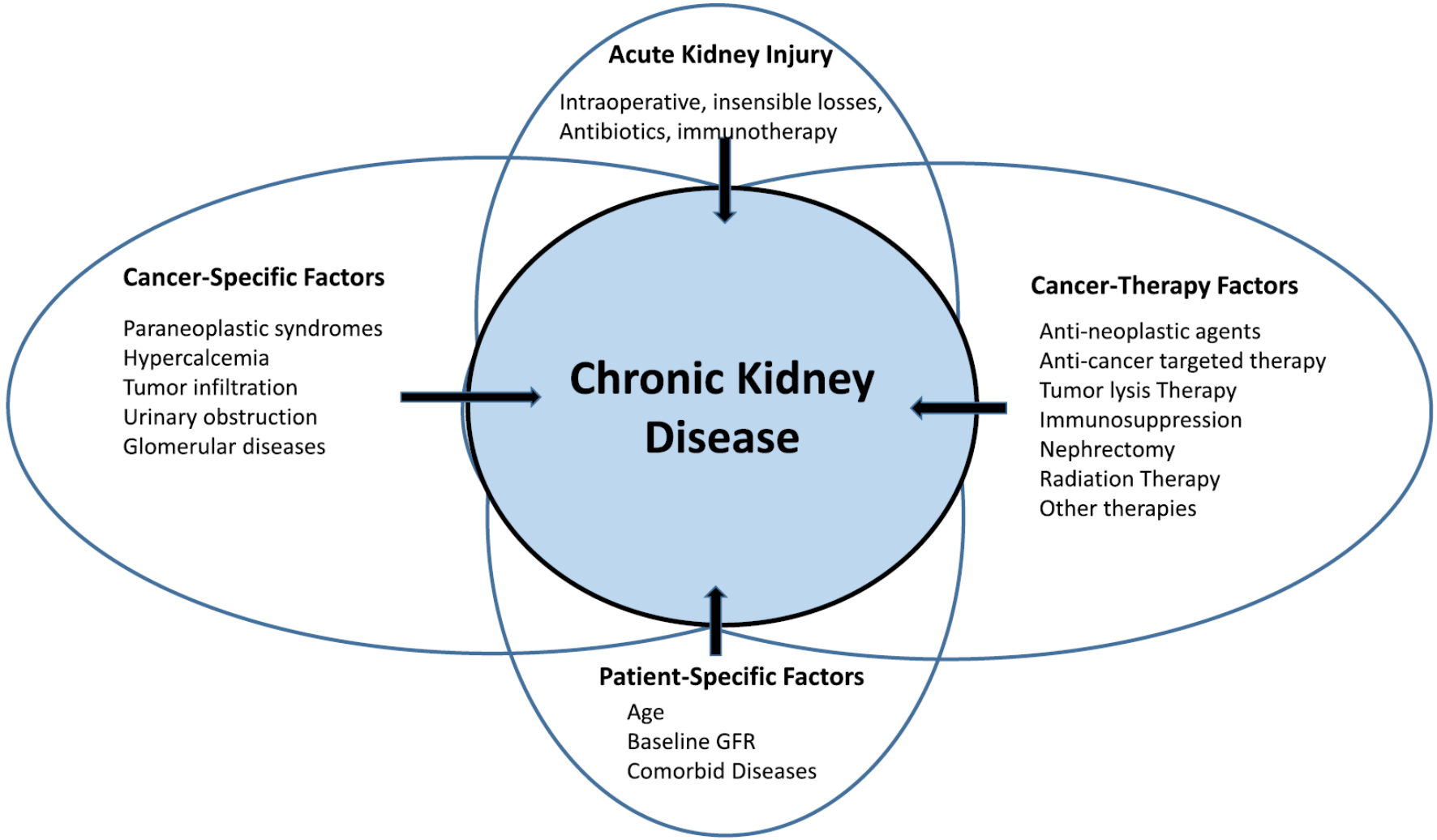



FIGURE 10. Risk Factors for Development of Chronic Kidney Disease (CKD) in Patients With Malignancy. GFR indicates glomerular filtration rate.

Am J Transl Res 2022;14(4):2356-2366
www.ajtr.org /ISSN:1943-8141/AJTR0140920

*Original Article*

# Association between chronic kidney disease and cancer including the mortality of cancer patients: national health and nutrition examination survey 1999-2014

Kanglin Guo*, Zufeng Wang*, Ran Luo, Yichun Cheng, Shuwang Ge, Gang Xu

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- **30559 participants** from NHANES **1999-2014**
- **2824 participants with cancer**.
- Subgroups were grouped by cancer location.

- The **three cancers with highest prevalence of CKD** were **kidney cancer** (72.3%), **bladder cancer** (54.7%), and **colon cancer** (43.0%) .
- The prevalence of CKD was **higher in cancer** patients compared to non-cancer patients.
- Only **genitourinary cancer** showed a **positive association with CKD (OR=1.23**, 95% CI: 1.05-1.44) after adjusting for confounding factors.
- However, **CKD was an independent risk factor for mortality from cancer** regardless of the type of cancer.
-

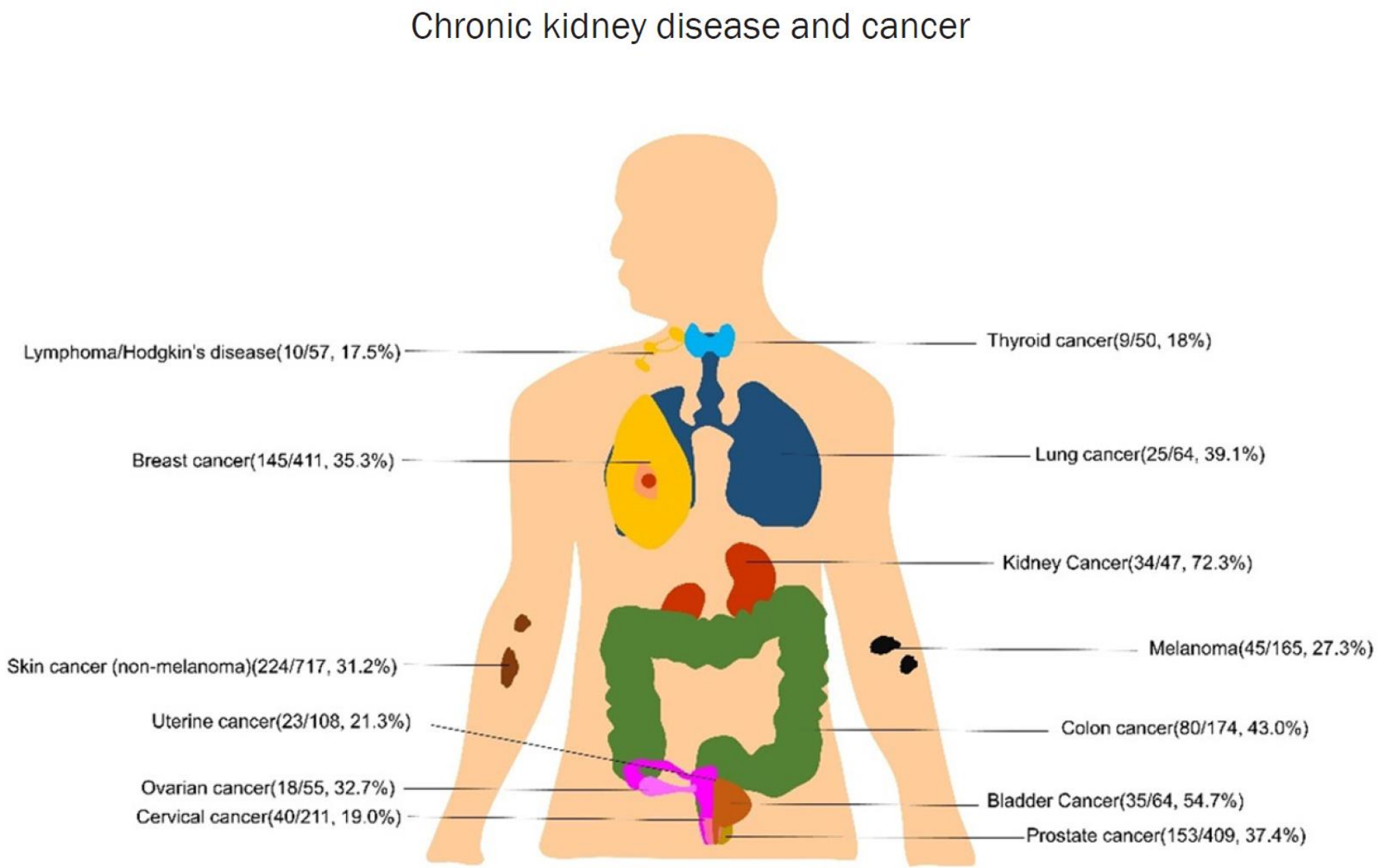


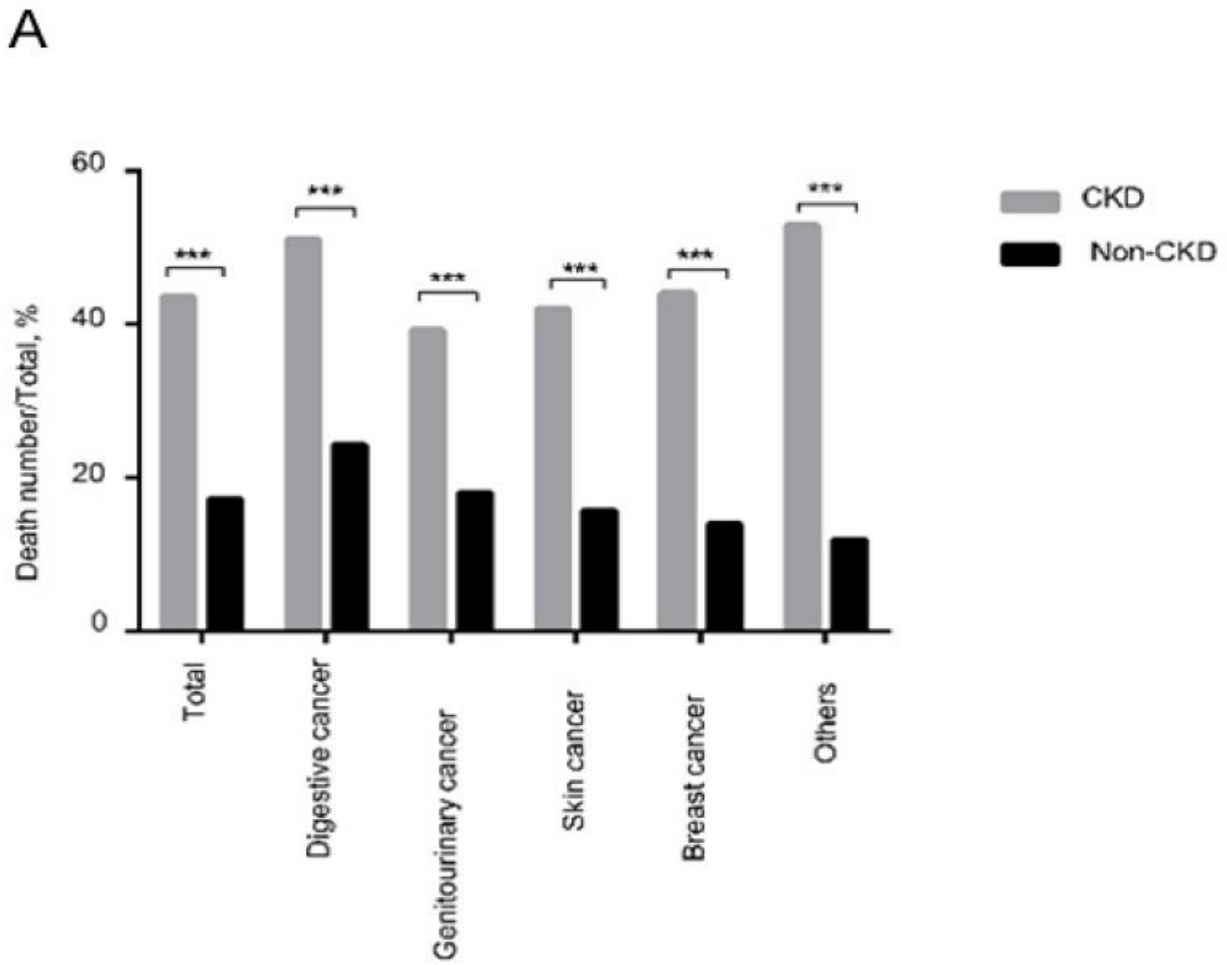

**Figure 2.** The body map of the incidence of CKD among different tumor patients. CKD: chronic kidney disease.

| | CKD/total number (%) | *p*-value | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|---|
| | | | OR | *p*-value | OR | *p*-value | OR | *p*-value |
| No-cancer | 4677/27735 (16.9%) | Ref | Ref | | Ref | | Ref | |
| Digestive cancer | 98/230 (42.6%) | <0.001 | 3.66 (2.81-4.76) | <0.001 | 1.32 (0.99-1.74) | 0.055 | 1.23 (0.91-1.65) | 0.173 |
| Genitourinary cancer | 306/911 (33.6%) | <0.001 | 2.49 (2.17-2.87) | <0.001 | 1.21 (1.04-1.41) | 0.016 | 1.23 (1.05-1.44) | 0.013 |
| Skin cancer | 269/882 (30.5%) | <0.001 | 2.16 (1.87-2.51) | <0.001 | 0.97 (0.82-1.14) | 0.698 | 0.94 (0.79-1.12) | 0.483 |
| Breast cancer | 145/411 (35.3%) | <0.001 | 2.69 (2.19-3.30) | <0.001 | 0.97 (0.78-1.22) | 0.805 | 0.89 (0.70-1.13) | 0.351 |
| Others | 51/212 (24.1%) | 0.006 | 1.56 (1.14-2.14) | 0.006 | 0.91 (0.64-1.28) | 0.581 | 0.83 (0.58-1.20) | 0.324 |
| Total cancer | 916/2824 (32.4%) | <0.001 | 2.37 (2.17-2.58) | <0.001 | 1.07 (0.97-1.18) | 0.184 | 1.04 (0.94-1.15) | 0.419 |

Model 1: Unadjusted; Model 2: Adjusted for age, sex, marital status, race/ethnicity, education level, and category of income; Model 3: Additional adjusted for hypertension, diabetes, alcohol consumption, smoking status, body mass index, high-density lipoprotein cholesterol, total cholesterol, triglyceride, and uric acid. CKD: chronic kidney disease.

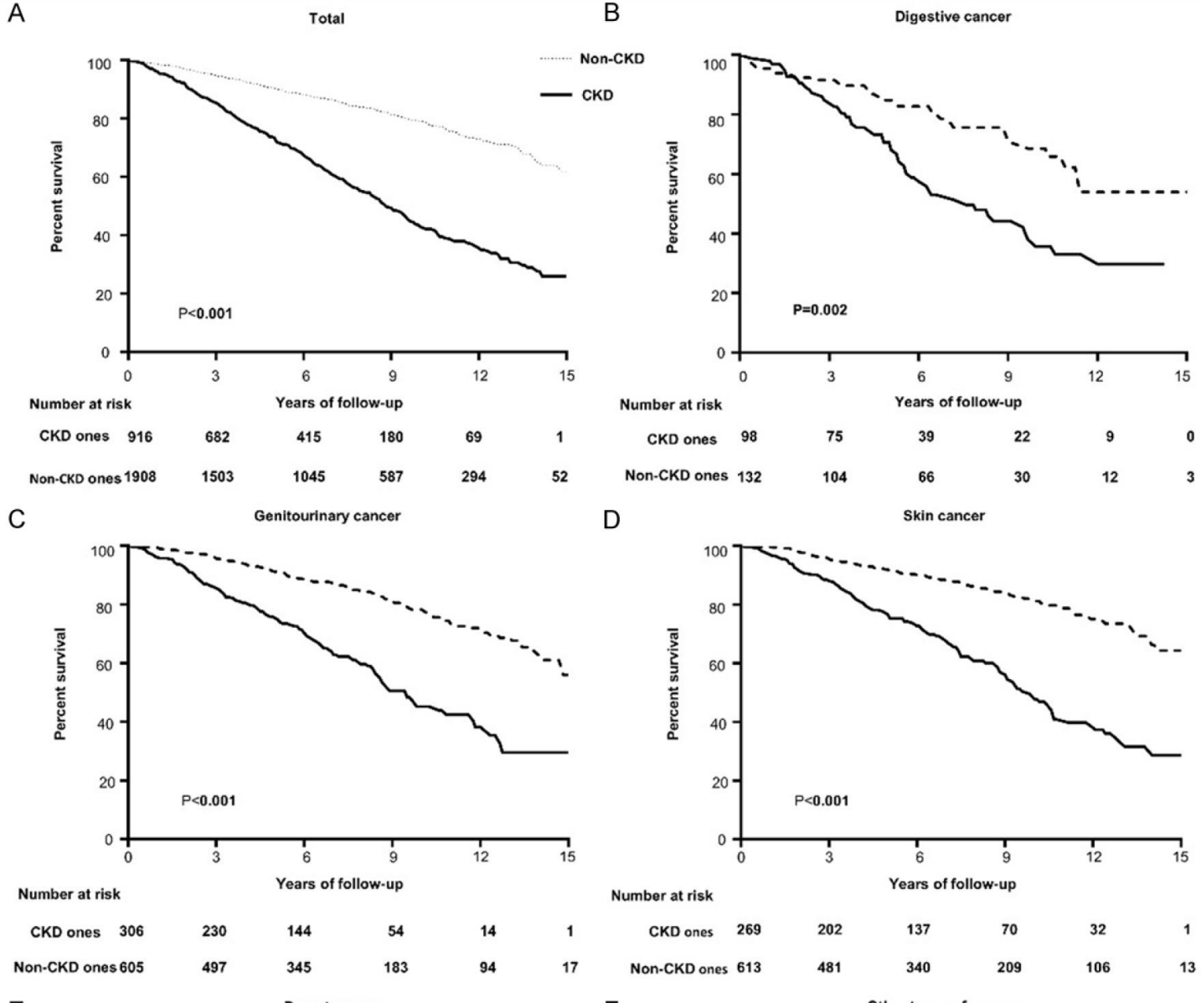
Am J Transl Res 2022;14(4):2356-2366

# A: The different mortality of cancer patients with or without CKD.




Am J Transl Res 2022;14(4):2356-2366

# Mortality is related to CKD status among all cancer patients and different cancer types.



Cancer
An International Interdisciplinary
Journal of the American Cancer Society

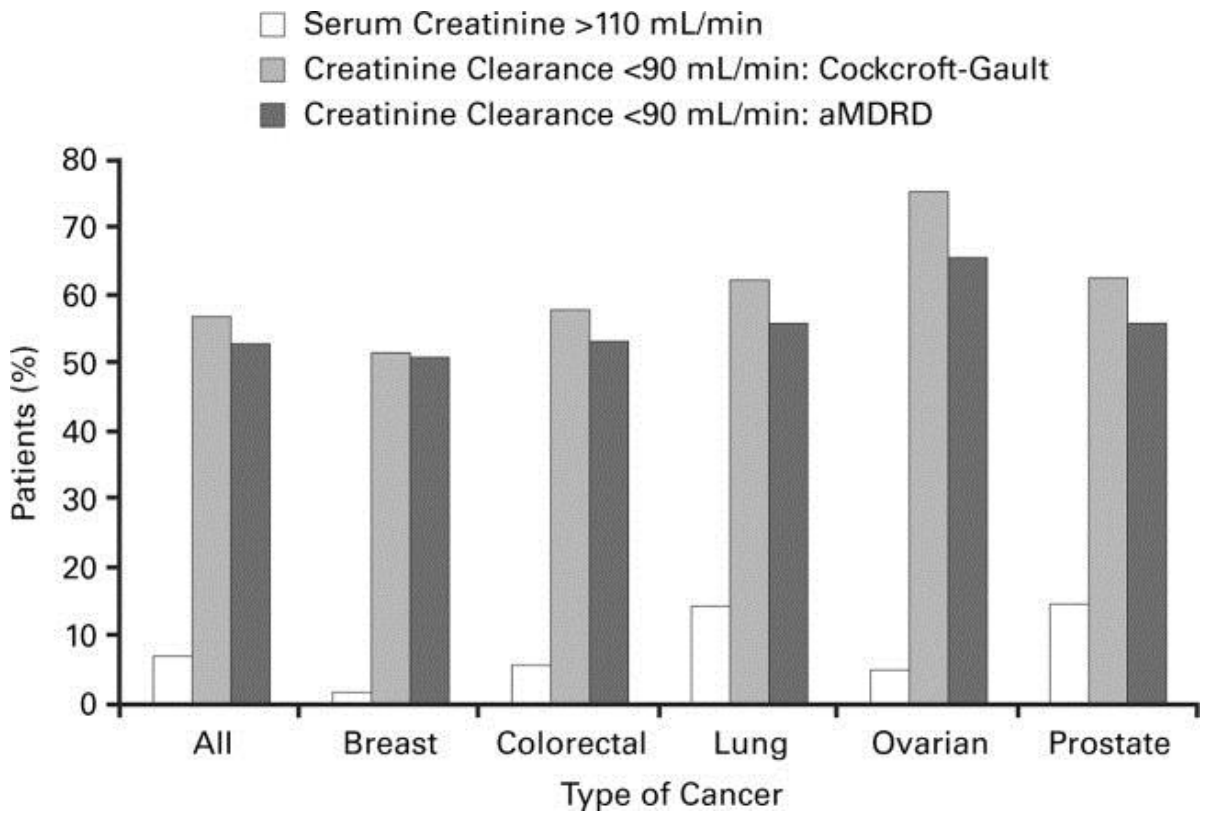
Original Article | Free Access

# Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management

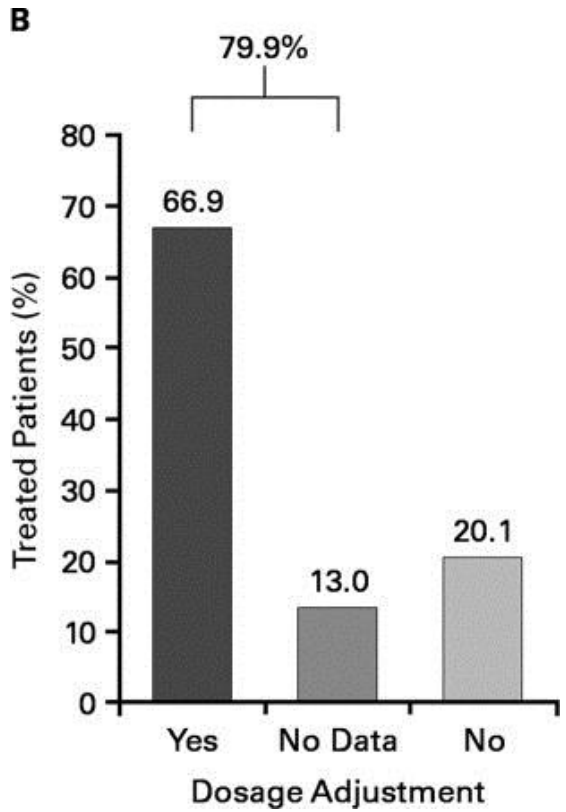
## The renal insufficiency and anticancer medications (IRMA) study

Vincent Launay-Vacher PharmD ✉, Stéphane Oudard MD, Nicolas Janus PharmD, Joseph Gligorov MD, Xavier Pourrat PharmD, Olivier Rixe MD, Jean-François Morere MD, Philippe Beuzeboc MD, Gilbert Deray MD,
On behalf of the Renal Insufficiency and Cancer Medications (IRMA) Study Group

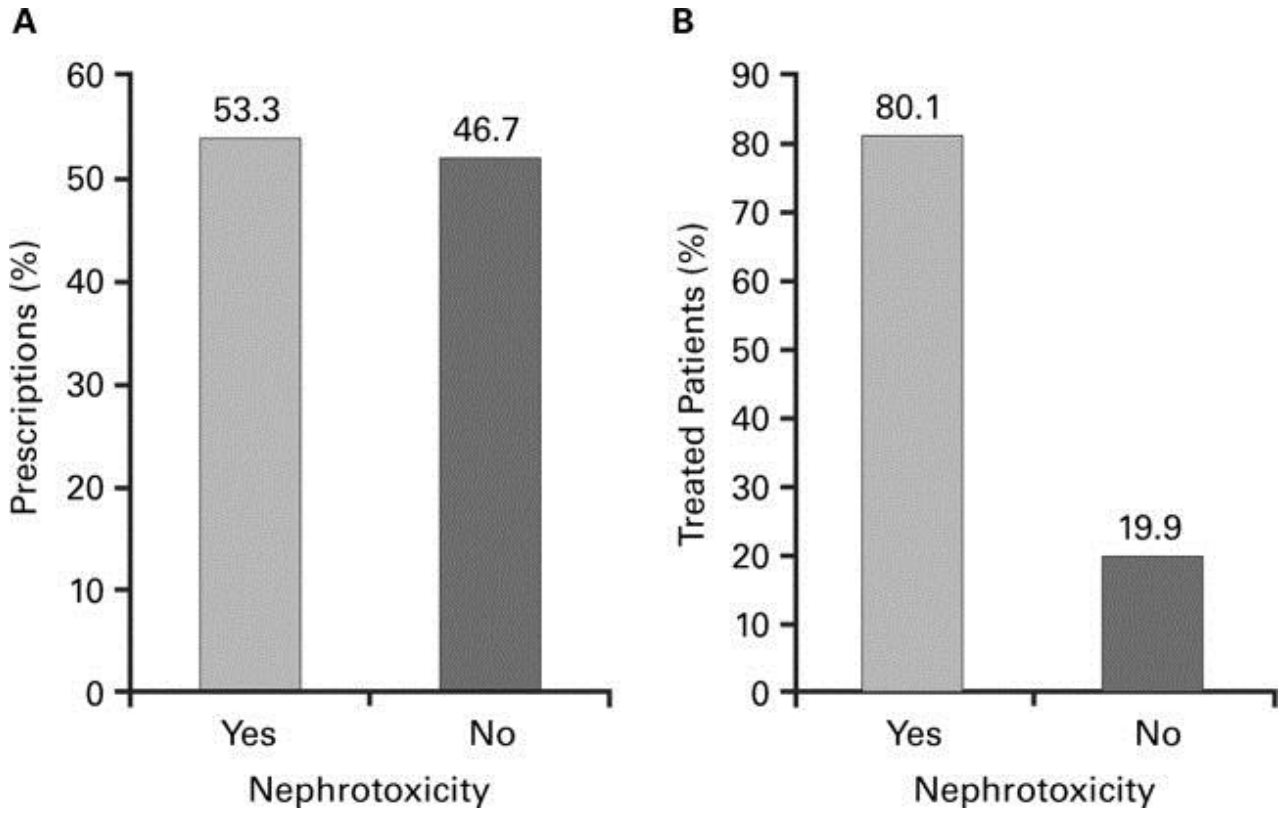
Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management




Cancer, Volume: 110, Issue: 6, Pages: 1376-1384, First published: 31 August 2007, DOI: (10.1002/cncr.22904)




Cancer, Volume: 110, Issue: 6, Pages: 1376-1384, First published: 31 August 2007, DOI: (10.1002/cncr.22904)




Cancer, Volume: 110, Issue: 6, Pages: 1376-1384, First published: 31 August 2007, DOI: (10.1002/cncr.22904)

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 |

# Epidemiology of chronic kidney disease in cancer patients: lessons from the IRMA study group

Vincent Launay-Vacher [1]

Affiliations + expand

PMID: 21146120 DOI: 10.1016/j.semnephrol.2010.09.003

Observations performed in IRMA-2 showed that the **survival rate at 2 years** was significantly **lower for patients with KD** (aMDRD<60).
This reduced survival has been hypothesized to be related to the **cardiovascular** complications of KD or as a consequence of **inappropriate drug dosage adjustment**.

Semin Nephrol . 2010 Nov;30(6):548-56.

# Chronic kidney disease and risk of kidney or urothelial malignancy: systematic review and meta-analysis

What is the risk of incident urinary tract malignancy among persons with CKD?

## Methods

**Systematic search**
3,035 records identified
6 observational studies included

**Chronic kidney disease**
eGFR <60 mL/min/1.73 $m^2$
or diagnostic code for CKD

**Outcomes of interest**
Cancer diagnosis of the kidney, renal pelvis, ureters, urinary bladder, and urethra

## Results

8,617,563 subjects
982,236 subjects with CKD

13,708 kidney cancer cases
13,772 urothelial carcinoma cases

| | Kidney cancer | Urothelial carcinoma |
|---|---|---|
| **IRR** (incidence rate ratio) | **3.36** (2.32–4.88) | **3.96** (2.44–6.40) |
| **aHR** (adjusted hazard ratio) | **2.04** (1.77–2.36) | **1.35** (1.22–1.50) |

Brooks, E. *et al.*
NDT (2023)
@NDTSocial

**Persons with non-dialyzed CKD have a higher unadjusted incidence and adjusted risk of urinary tract malignancy compared to those with preserved kidney function.**

RESEARCH ARTICLE

# Risk of malignancy in patients with chronic kidney disease

**Ketki K. Tendulkar[1]*, Brendan Cope[2], Jianghu Dong[1,3], Troy J. Plumb[1], W. Scott Campbell[4], Apar Kishor Ganti[5]**

**Table 1. Patient characteristic summary by stage of CKD.**

| | All cohort (N = 13,750) | > = 60 (N = 282) | 45–59 (N = 8,197) | 30–44 (N = 2,940) | <30 (N = 2,331) | P value |
|---|---|---|---|---|---|---|
| Male (%) | 53 | 54 | 54 | 49 | 53 | <0.001 |
| Race (%) | | | | | | <0.001 |
| White | 80.5 | 80.5 | 79.5 | 82.9 | 81.7 | |
| AA Black | 13.6 | 14.9 | 15.6 | 11.3 | 10.0 | |
| Hispanic | 2.4 | 1.4 | 2.1 | 2.3 | 3.4 | |
| Others | 3.5 | 4.2 | 2.8 | 3.5 | 4.9 | |
| Age (%) | | | | | | <0.001 |
| <50 | 22.5 | 28.7 | 23.0 | 17.1 | 27.2 | |
| 50–65 | 33.5 | 50.7 | 36.5 | 29.1 | 26.4 | |
| 66–80 | 29.1 | 15.9 | 28.0 | 33.5 | 29.4 | |
| >80 | 14.9 | 4.6 | 12.5 | 20.3 | 17.0 | |
| Diabetes (%) | 48.3 | 42.8 | 55.3 | 45.5 | 45.3 | <0.001 |
| Hypertension (%) | 99.7 | 99.9 | 99.9 | 99.8 | 99.7 | 0.009 |
| CAD (%) | 36.9 | 30.1 | 39.1 | 39.6 | 27.7 | <0.001 |
| Smoking history (%) | 50.0 | 49.5 | 49.7 | 48.6 | 53.6 | <0.001 |
| BMI (%) | | | | | | <0.001 |
| <18.5 | 8.3 | 3.9 | 4.7 | 9.0 | 20.8 | |
| 18.5–24.9 | 20.0 | 17.4 | 19.4 | 21.0 | 21.3 | |
| 25.0–29.9 | 27.1 | 29.9 | 28.6 | 27.1 | 21.4 | |
| > = 30 | 44.5 | 48.7 | 47.3 | 42.9 | 26.5 | |

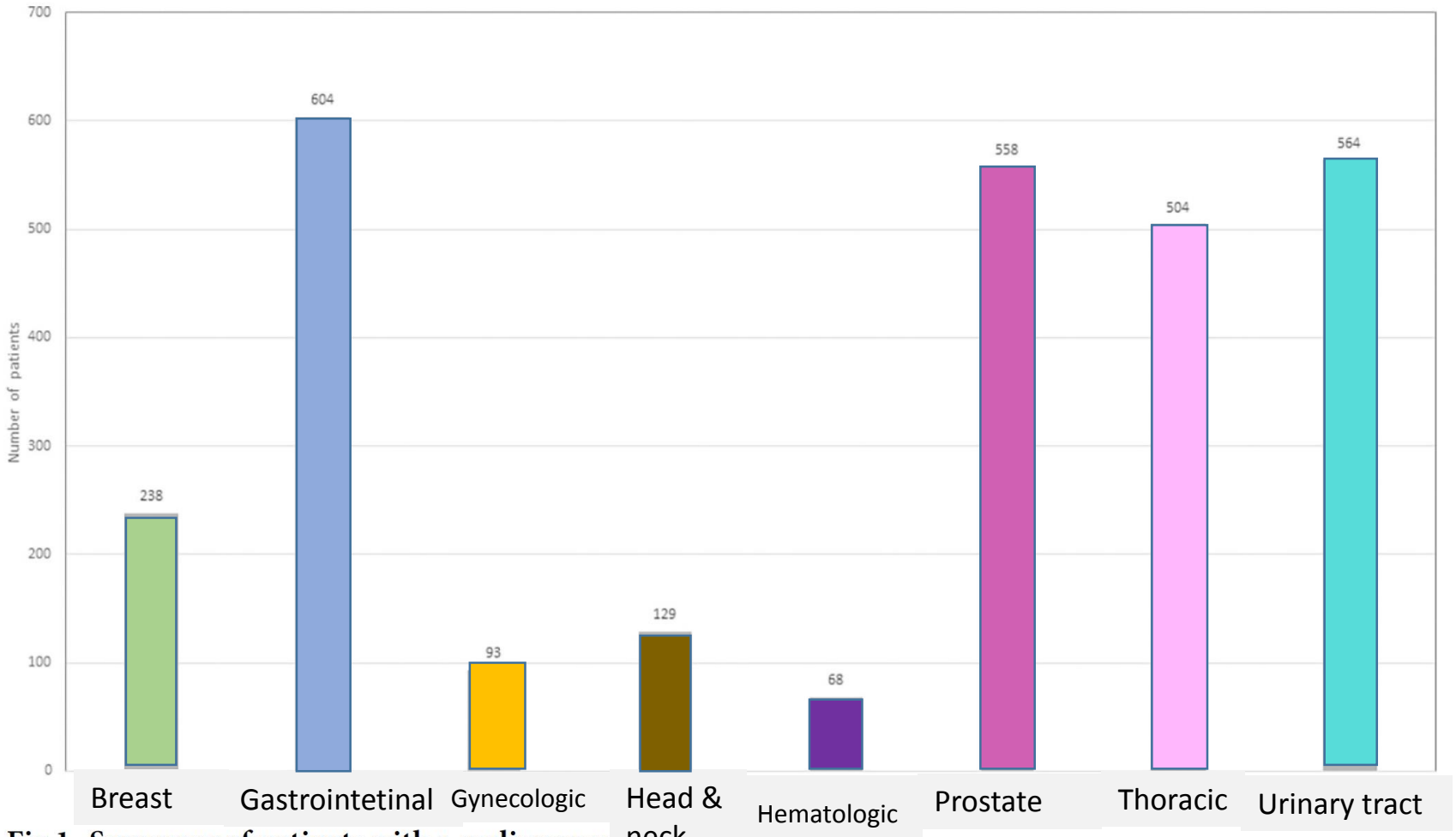



**Fig 1. Summary of patients with a malignancy**

https://doi.org/10.1371/journal.pone.0272910.g001

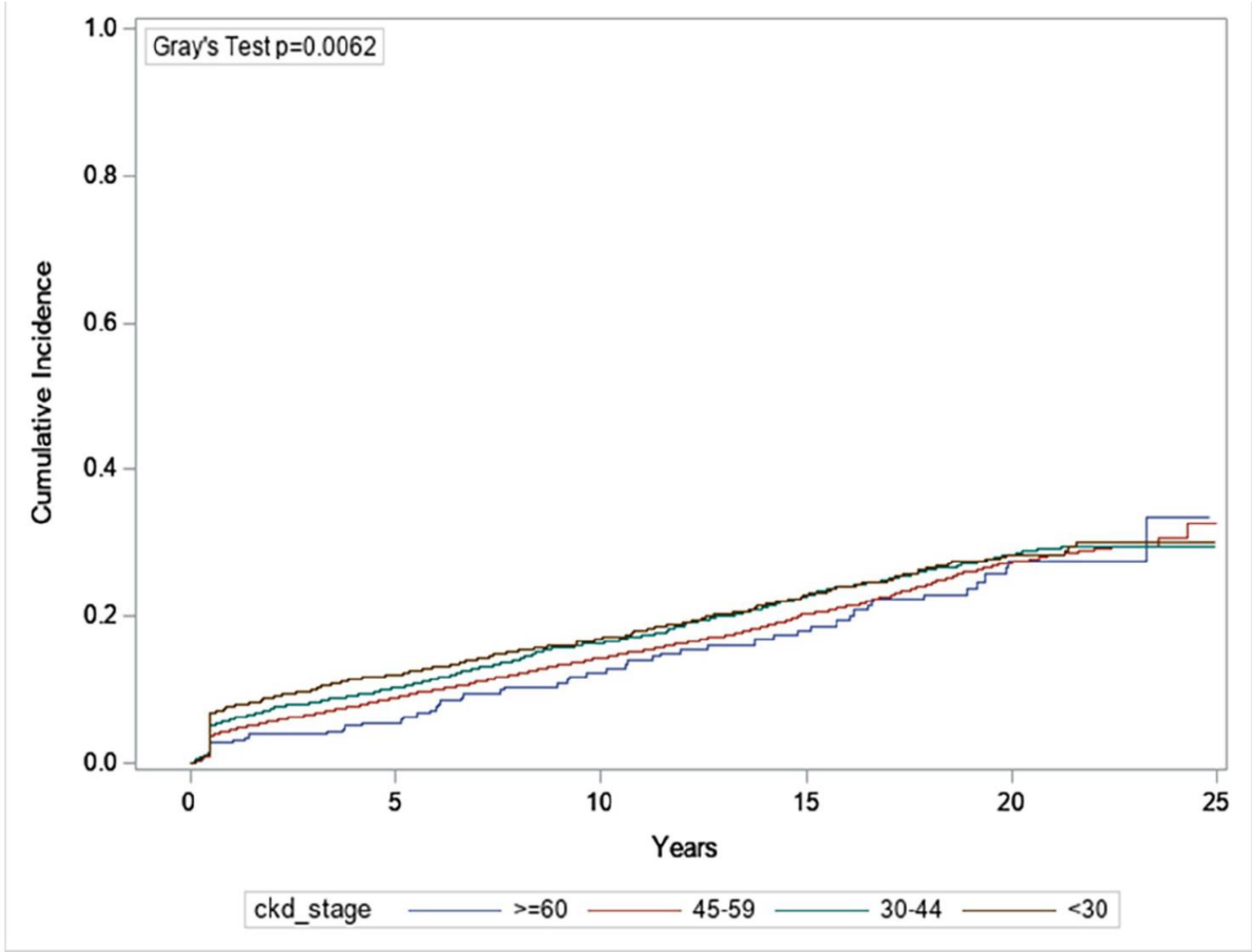



**Fig 5. The cumulative incidence of overall malignancy by CKD stage.**

**Table 2. Factors affecting the development of malignancy after CKD diagnosis.**

| | Hazard Ratio (95% CI) | P value |
|---|---|---|
| Age | | |
| <50 | 1.00 | |
| 50–65 | 2.23 (1.98, 2.51) | <0.001 |
| 66–80 | 3.15 (2.78, 3.56) | <0.001 |
| >80 | 3.34 (2.89, 3.88) | <0.001 |
| Male | 1.44 (1.33, 1.56) | <0.001 |
| Race | | |
| White | 1.00 | |
| AA Black | 0.92 (0.82, 1.03) | 0.161 |
| Hispanic | 0.84 (0.65, 1.08) | 0.193 |
| Others | 1.17 (0.96, 1.42) | 0.109 |
| Diabetes | 0.90 (0.83, 0.98) | 0.003 |
| CAD | 0.85 (0.80, 1.01) | 0.051 |
| Smoking history | 1.18 (1.09, 1.28) | <0.001 |
| BMI | | |
| <18.5 | 0.96 (0.81, 1.13) | 0.297 |
| 18.5–24.9 | 1.00 | |
| 25.0–29.9 | 1.07 (0.96, 1.20) | 0.888 |
| > = 30 | 1.02 (0.93, 1.17) | 0.631 |
| Range of eGFR | | |
| > = 60 | 1.00 | |
| 45–59 | 1.06 (0.81, 1.39) | 0.631 |
| 30–44 | 1.25 (0.95, 1.65) | 0.102 |
| <30 | 1.44(1.08,1.91 | 0.004 |

# Chronic Kidney Disease and Cancer: Inter-Relationships and Mechanisms

*Mengsi Hu[1,2†], Qianhui Wang[1†], Bing Liu[1,2], Qiqi Ma[1], Tingwei Zhang[1], Tongtong Huang[1], Zhimei Lv[1,2*] and Rong Wang[1,2*]*

[1]*Department of Nephrology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China,*
[2]*Department of Nephrology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China*

Front. Cell Dev. Biol. 10:868715.
doi: 10.3389/fcell.2022.868715

- Globally, the **incidence** of (**CKD**) and **death due to CKD** have increased by **89** and **98%,** respectively, from 1990 to 2016.(1)

- A **large cohort study of CKD** from the United Kingdom showed that **malignant tumors** might be one of the leading causes of non-cardiovascular death in patients with **CKD stage G3-G5**, accounting for **15% of all deaths** in this population.(2)

- The number of **cancer survivors** has significantly risen, whereas this population might also be **suffering a high risk of CKD**. (3)

1.Xie, Y., et al.. Kidney Int. 94, 567–581. doi:10.1016/j.kint.2018.04.011
2. Marks, A.,et al,.. Fam. Pract. 30, 282–289. doi:10. 1093/fampra/cms079
3. Shin, H.-Y., et al,.. Asian Pac. J. Cancer Prev. 16, 1355–1360. doi:10.7314/apjcp.2015.16.4.

# POTENTIAL MECHANISMS OF INCREASED CANCER INCIDENCE RATE IN CKD PATIENTS

- An analysis of datafrom the **United States, Europe, Australia**, and **New Zealand** on renal and urethral cancer in end-stage dialysis patients showed that increased risk of **renal parenchymal cancer** in **ESKD patients** was consistent with **loss of renal function** and **its duration.**
- The incidence rate of cancer incidence in **renal transplant patients** with ESKD **tripled** that of patients before renal transplantation, which might be attributed **to immune suppression** and **oncogenic virus infection**.

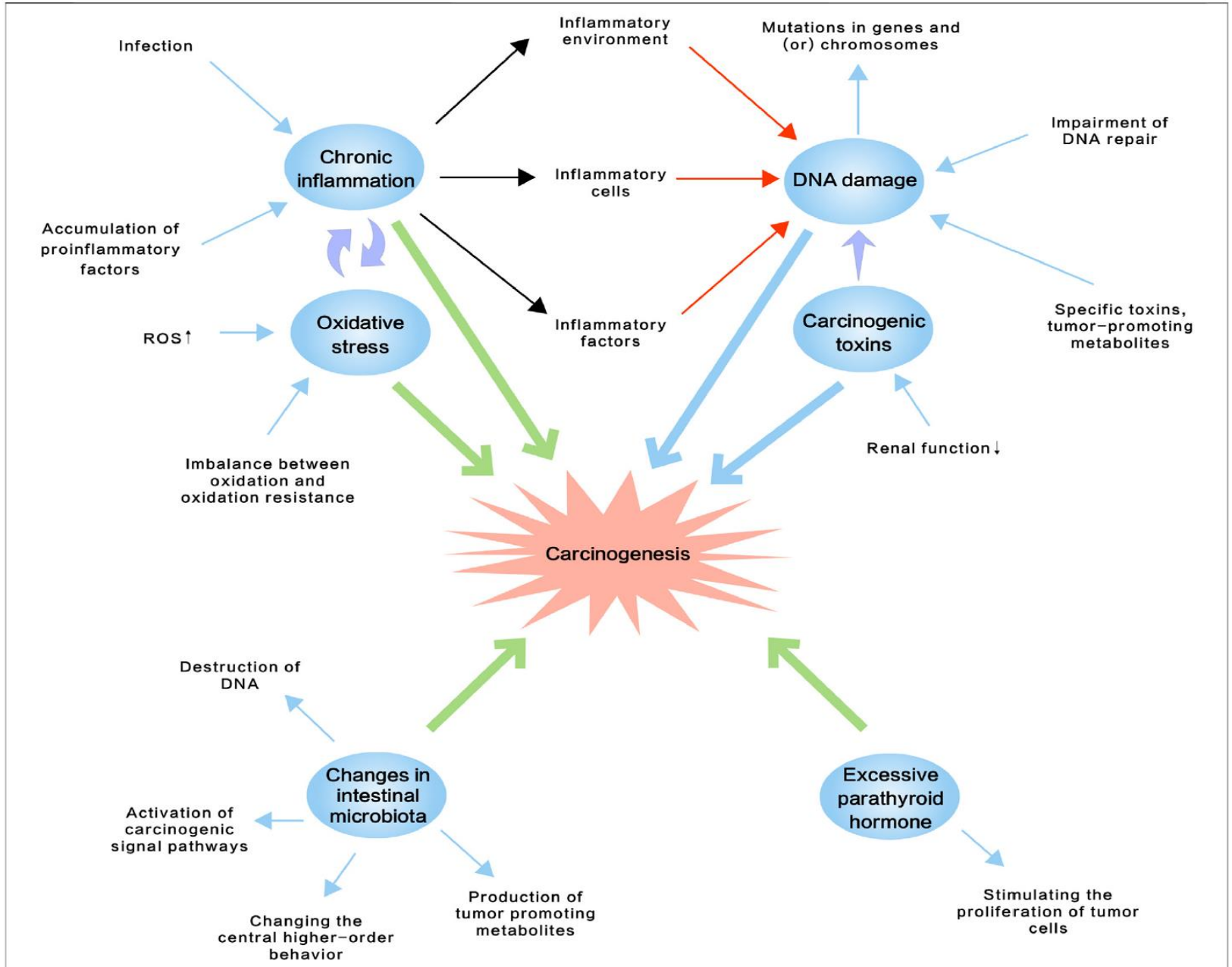



**FIGURE 1 |** Schematic diagram of potential molecular mechanisms of the relatively high incidence rate of cancer in CKD, which might include chronic inflammation, accumulation of carcinogenic compounds, oxidative stress, impairment of DNA repair, excessive parathyroid hormone and changes in intestinal microbiota. ROS, reactive oxygen species.

# Changes in Intestinal Microbiota

- Alarge number of studies reported that **lactobacilli decreased** in the intestinal microbiota of **CKD animals and patients**, while **Enterobacteriaceae** with a **gene encoding tryptophan tyrosine phenol lyase** increased, demonstrating they might come into play in **production of uremic toxins** (Kikuchi et al., 2017).

- As mentioned earlier, **AHR** was a ligand activated transcription factor known for its **tumor-promoting effects**, and **uremic toxins derived from intestinal microbiota** have been recognized as effective **endogenous ligands for AHR activation** (Murray et al., 2014).

- Other mechanisms have been proposed that the **imbalance of intestinal flora** might aggravate the **development of intestinal tumors** and **inhibit antitumor immunity**, and might be related to the followings:
- 1) **destruction of DNA**: This might arise by the injury induced by intestinal flora producing **specific toxins like Colibactin**;
- 2) **activation of carcinogenic signal pathways**, including **PI3K/Akt**, **Wnt** and **NF-κB signaling pathways**, which were activated by the toxins expressed by Helicobacter pylori; and
- 3) **production of tumor-promoting metabolites such** as **secondary bile acids**, secreted or produced by coupled binding of bile acids by intestinal microbiota (Mima et al., 2017).

# Impact of Cancer on Kidneys

- Chemotherapy and radiation
- TLS
- Metastasis
- Paraneoplastic Syndromes
- Obstruction

# Nephrectomy

- **Reduction of healthy parenchymal** volume after nephrectomy
- might lead to **compensatory hypertrophy** and **over filtration** of
- the remaining kidney, as 50% of the nephron was lost, which
- could result in **glomerulosclerosis**, **proteinuria**, hypertension and **decrease in renal function** in the long run.
- Therefore, the
- Therefore preservation of healthy renal parenchyma and long-term
- follow-up was of great significance to prevent the occurrence
- of CKD after nephrectomy.

# Onconephrology: Core Curriculum 2023

*Niloufarsadat Yarandi and Anushree C. Shirali*

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# Measurement of Kidney Function in Cancer Patients

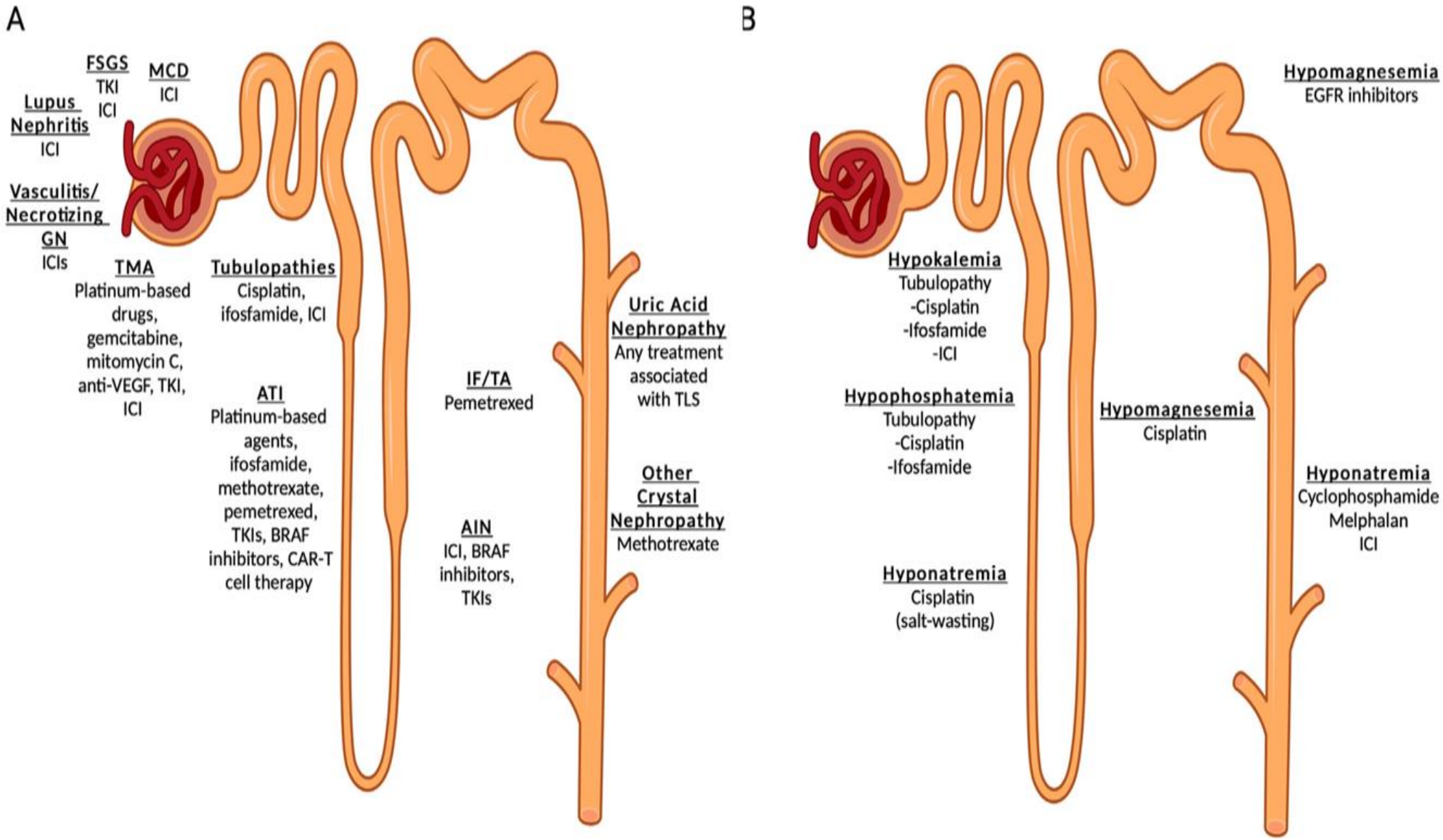
- GFR remains widely accepted as the best index for kidney function.
- eGFR)-creatinine are confounded by factors
- **cachectic sarcopenia**
- **variable protein intake**
- , which may lead to an overestimation of the actual GFR.
- Additionally, because **tubular secretion** contributes to urinary creatinine excretion, drugs such as **trimethoprim,Cyclin dependent kinase 4/6** which inhibit secretory pathways for creatinine, raise creatinine levels without affecting GFR.

- The same may be true in the cancer population although some **cancers** **secrete cystatin C** and some drugs including **corticosteroids** may also increase cystatin C levels.
- **Inulin clearance** is the gold standard for measured GFR, but it is not used in clinical practice.
- Measured clearances of $^{125}$I-iothalamate or iohexol are acceptable because they also undergo glomerular filtration without tubular secretion, reabsorption, or metabolism.

# Nephrotoxicity of Anticancer Therapy

| Drug | Type of Kidney AEs | Mechanism of Kidney AEs | Prevention and Treatment |
|---|---|---|---|
| Platinum agents | AKI-ATN (Cis>>Carbo>Oxali), Fanconi syndrome, hyponatremia, hypomagnesemia | ATN: direct tubular toxicity | Volume expansion, magnesium repletion |
| Ifosfamide | AKI-ATN, hemorrhagic cystitis, NDI | ATN: direct tubular toxicity; hemorrhagic cystitis: bladder injury | Volume expansion/mesna for hemorrhagic cystitis |
| Cyclophosphamide | Hyponatremia, hemorrhagic cystitis | Hyponatremia: increased tubular reabsorption of water/? ADH secretion; hemorrhagic cystitis: bladder injury by metabolite | Volume expansion/mesna for hemorrhagic cystitis |
| Bendamustine | AKI-ATN, NDI, Gitelman | ATN: direct tubular toxicity | |
| Melphalan | AKI, hyponatremia | SIADH | SIADH: drug withdrawal, usual approach to SIADH |
| Methotrexate | AKI | Intratubular crystal formation | Volume expansion, urine pH > 7.0, stop PPI, NSAIDs |
| Pemetrexed | AKI | Acute tubular necrosis, progressive interstitial fibrosis, nephrogenic diabetes insipidus, and distal renal tubular acidosis | Folic acid and vitamin $B_{12}$, adequate hydration |
| Gemcitabine | AKI, hypertension, proteinuria | TMA | Drug withdrawal, complement inhibitors may be considered |
| Nitrosoureas | CCNU, Me-CCNU, BCNU: chronic interstitial nephritis, Streptozocin-Fanconi syndrome, AKI | Chronic interstitial nephritis: ? tubular cell protein alkylation; AKI: tubular injury | |
| Trabectedin | AKI | ? secondary to rhabdomyolysis | |
| Doxorubicin | AKI, hypertension, proteinuria | TMA | TMA: drug withdrawal |
| Mitomycin C | AKI, hypertension, proteinuria | TMA | TMA: drug withdrawal, ? eculizumab |
| Vinca alkaloids | AKI, hypertension, proteinuria, hyponatremia | TMA, SIADH | TMA: drug withdrawal; SIADH: drug withdrawal |

Abbreviations: ADH, antidiuretic hormone; AE, adverse event; AKI, acute kidney injury; ATN, acute tubular necrosis; BCNU, carmustine; Carbo, carboplatin; CCNU, lomustine; Cis, cisplatin; Me-CCNU, methyl-CCNU, semustine; NDI, nephrogenic diabetes insipidus; NSAID, nonsteroidal anti-inflammatory drug; Oxali, oxaliplatin; PPI, proton pump inhibitor; SIADH, syndrome of inappropriate diuresis; TMA, thrombotic microangiopathy.


A
FSGS
TKI
ICI
MCD
ICI
Lupus Nephritis
ICI
Vasculitis/ Necrotizing GN
ICIs
TMA
Platinum-based drugs, gemcitabine, mitomycin C, anti-VEGF, TKI, ICI
Tubulopathies
Cisplatin, ifosfamide, ICI
ATI
Platinum-based agents, ifosfamide, methotrexate, pemetrexed, TKIs, BRAF inhibitors, CAR-T cell therapy
IF/TA
Pemetrexed
AIN
ICI, BRAF inhibitors, TKIs
Uric Acid Nephropathy
Any treatment associated with TLS
Other Crystal Nephropathy
Methotrexate
B
Hypomagnesemia
EGFR inhibitors
Hypokalemia
Tubulopathy
-Cisplatin
-Ifosfamide
-ICI
Hypophosphatemia
Tubulopathy
-Cisplatin
-Ifosfamide
Hypomagnesemia
Cisplatin
Hyponatremia
Cisplatin
(salt-wasting)
Hyponatremia
Cyclophosphamide
Melphalan
ICI

# Platinum-based Chemotherapy

- Platinum-based Chemotherapy Cisplatin, carboplatin, and oxaliplatin These structurally different agents **cross-link DNA**, distorting the DNA helix and inducing **cell death**.
- Kidney effects include **dose-dependent nonoliguric AKI** from **ATN**, affecting up to **30%** of patients on cisplatin, particularly with **single-cycle dosing of >60 mg/m2** or **cumulative-cycle dosing of >300 mg/m2.**
- Drug cessation usually resolves ATN. AKI risk is highest with cisplatin, followed by carboplatin and oxaliplatin.
- **Hypomagnesemia, Fanconi syndrome**, **distal renal tubular acidosis**,**TMA** and hyponatremia from **salt wasting nephropathy** have been well described with cisplatin.(rare with carbo and oxaliplatin)

- **Prevention** of platinum drug nephrotoxicity starts with
- **volume expansion**.
- Cisplatin enters proximal tubule epithelial cells (PTECs) via transporters, including **organic cation transporter-2** whose expression is upregulated by hypomagnesemia.
- Limited data suggest that **magnesium repletion may** counteract cisplatin nephrotoxicity.

**Table 5.** Risk Factors for Anticancer Drug-induced Renal Toxicity: Example of Cisplatin

| Repeated administrations and frequent courses |
| --- |
| ✓Cumulative dose >450 mg/m$^2$ |
| ✓Pre-existing renal disease/abnormal renal function |
| ✓Dehydration |
| ✓Heart failure, adema, ascites, etc |
| ✓Anemia |
| ✓Coadministration of other nephrotoxic agents |
| ✓Dosage not adjusted to the level of renal function |

# Ifosfamide

- Ifosfamide is an alkylating agent used against pediatric and adult **sarcomas**, **testicular cancer**, and other conditions.
- Nephrotoxic metabolite **chloroacetaldehyde** causes **ATN** and **Fanconi** syndrome, particularly with concurrent cisplatin use.
- **Nephrogenic diabetes** insipidus has also been described.
- **Volume expansion** is the only prophylaxis.
- **Childhood survivors** of cancer requiring ifosfamide treatment may develop subsequent **CKD**, particularly if their **cumulative ifosfamide exposure** was **>84 g/m2.**

- Ifosfamide may also cause **hemorrhagic cystitis**, for which sodium 2-mercaptoethane sulphonate (**mesna) provides prophylaxis**.

# Cyclophosphamide

- Structurally similar to ifosfamide, cyclophosphamide.
- The **metabolites are different** than ifosfamide, explaining why **ATN is rare** with cyclophosphamide.
- **Hemorrhagic cystitis** does occur, and intravenous dosing requires mesna prophylaxis.
- Cyclophosphamide is also associated with **hyponatremia**.
- The mechanism is not fully elucidated, but
- **increased ADH secretion**,
- **up-regulation of the V2** 746 receptor,
- **increased aquaporin permeability** have been proposed.

# Methotrexate

- Used against osteosarcomas, leukemias, and lymphomas,
- Methotrexate inhibits **dihydrofolate reductase** and **thymidine synthase**, **reducing the availability of nucleotides necessary for cell division**.
- **High-dose intravenous methotrexate (HDMTX: >0.5 g/ m2) vasoconstricts afferent arterioles** and forms **intratubular crystals** when **urine is acidic** and **urine flow is low**.
- Both mechanisms lead to **nonoliguric and reversible AKI**.

- **NSAIDs, penicillins**, and **proton pump inhibitors (PPIs)** interfere with drug transporter elimination of methotrexate and **should be avoided with HDMTX**.
- **Alkali-containing crystalloids** to generate **urine pH >7.0** and **urine output > 2.5** L/day are essential.
- **Highdose leucovorin within 18-42 hours of HDMTX** provides folate rescue.

- This is critical to prevent and treat renal and extrarenal methotrexate toxicity, but **efficacy wanes at methotrexate levels of >10 µM**.
- After HDMTX infusion, the drug levels should be monitored until levels decrease < 0.1 µM.
- **Hemodialysis may be necessary for prevention of extrarenal toxicities from high methotrexate levels in patients with AKI**.
- Methotrexate is **partly protein bound**, which is not ideal for extracorporeal removal, and **postdialysis drug** levels also commonly **rebound**.

- The recombinant **enzyme glucarpidase** reduces plasma methotrexate concentrations by up to **99% within 15 minutes of** administration without plasma rebound.
- Glucarpidase is approved by the US Food and Drug Administration for **delayed methotrexate clearance with HDMTX-associated kidney impairment**.
- The former is defined by expert guidelines as plasma methotrexate **levels of >50 µM, >30 µM,>10 µM, and>5 µM** at **24, 36, 42, and 48** hours after HDMTX dosing, respectively.

# Pemetrexed

- Pemetrexed is a **methotrexate analog** that is approved for non–small cell lung cancer (**NSCLC**) and **mesothelioma**, **often concurrently with cisplatin**.
- **Direct tubular toxicity** of pemetrexed causes
- **ATN**,
- **nephrogenic diabetes insipidus**,
- **distal RTA**
- Dosing in patients with **CLcr < 45 mL/min is contraindicated**.
- **Volume expansion** as well as **vitamin B12 and folate supplementation** are **preventive** measures.
- Drug cessation usually stabilizes or reverses AKI.
- Some patients with **higher cumulative dosing** and **exposure** will develop **CKD from progressive interstitial fibrosis**.

# Gemcitabine

- Gemcitabine is an **antimetabolite** used in **ovarian cancer**, **pancreatic** cancer, and other **solid tumors**.
- It is associated with **TMA**, with incidences estimated at **0.31%-1.4%.** Patients may develop **systemic TMA** characterized by microangiopathic hemolytic anemia, thrombocytopenia, proteinuria, and AKI or **kidney limited TMA with AKI/proteinuria**.
- **New onset or worsening of hypertension may herald TMA.**
- **Stopping gemcitabine** stabilizes or improves kidney disease in most patients.
- Plasma exchange does not have a role unless there is **another consideration, such as autoantibodies to complement factor H** that predisposed the patient to TMA.

- Complement inhibition with **eculizumab** has been **successful** with good kidney and hematological outcomes in small case series and isolated case reports, and this warrants **consideration in refractory cases of gemcitabine-TMA.**

# Targeted Agents

## Vascular Endothelial Growth Factor Inhibitors

- (VEGF) inhibitors target VEGF pathways to **inhibit tumor angiogenesis** in a variety of cancers.
- They include :

- **antibodies (bevacizumab**)
- **soluble receptors (aflibercept**) against circulating VEGF
- **antibodies** (**ramucirumab**) against **VEGF receptors** (**VEGF-R**).

# Vascular Endothelial Growth Factor Inhibitors

- **Podocyte-specific VEGF expression** is integral to the function of the glomerular basement membrane and glomerular endothelium.

- Additionally, circulating **VEGF promotes pressure natriuresis**, lymphangiogenesis, and **nitric oxide signaling**.
-
- Collectively, VEGF inhibition is associated with **dose-dependent hypertension**, **proteinuria**, and **systemic or kidney-limited TMA**.
- Kidney biopsy may reveal **TMA**, but minimal change disease **(MCD)** and focal and segmental glomerulosclerosis **(FSGS)** have also been described.

- Hypertension rates for VEGF inhibitors range from **19% to 30%** in large meta-analyses of clinical trials.
- **Dihydropyridine CCB** or **(RAAS) inhibitors** are the first line of treatment for hypertension due to VEGF inhibitors.
- Treatment can continue with controlled hypertension and subnephrotic proteinuria.
- For drug-attributed **TMA** or **nephrotic proteinuria**, **discontinuation is necessary** and usually reverses kidney toxicity.

# Tyrosine Kinase Inhibitors

- Small-molecule TKIs prevent activation of receptor, cytoplasmic, or dual-specificity tyrosine kinases (TK), inhibiting signaling pathways for cell growth, migration, and apoptosis.
- Depending on the **specific TK targets** (**VEGF**, **epidermal growth factor receptors**, **anaplastic lymphocyte kinase**, etc), there are variable side effects of TKIs.

- For example, **sunitinib, sorafenib, axitinib, cabozantinib**, and others downstream of VEGF are associated with **hypertension and proteinuria**, either **isolated or with TMA**.
- Other kidney lesions include **MCD, FSGS** from healed TMA, acute tubulointerstitial nephritis (**AIN**), and **chronic interstitial nephritis**.

- Electrolyte disorders, including **hypocalcemia**, **hypophosphatemia**, and **hypomagnesemia**, are seen in varying degrees with many multitarget TKIs.
- **Vandetanib** has been **associated with all 3 of these electrolyte** derangements.

# BRAF Inhibitors

- Serine-threonine kinase B-rapidly activated fibrosarcoma (BRAF) inhibitors, including **dabrafenib** and **vemurafenib**, target the BRAF protein, which **activates the mitogen-activated protein kinase (MAPK)** pathway.
- **Melanoma** and other tumors with **specific BRAF mutations** have pro-oncogenic signaling, and inhibition of the BRAF and MAPK pathways is a potent antitumor treatment.
- These drugs have been associated with **AIN**, **ATN** with **Fanconi** syndrome, and **proteinuric podocytopathy** when used in combination with **MEK inhibitors**.

# EGFR Inhibitors

- These include **small molecule TKIs such as gefitinib, erlotinib**, and **afatinib** and monoclonal antibodies (mAbs) such as **cetuximab** and **panitumumab**.
- Anti-EGFR mAbs have a **high incidence of hypomagnesemia** via **inhibition** of transient receptor potential channel M6 (**TRPM6)**–mediated absorption of magnesium in the distal nephron.
- **Hypokalemia** and **hypophosphatemia** have also been less described.

- **Rare r**eports of glomerular lesions include **crescentic IgA** nephropathy, **immune-complex glomeru**lonephritis, and **pauci-immune crescentic** glomerulonephritis.

# Proteasome Inhibitors

- Primarily used as treatment for multiple myeloma, proteasome inhibitors (PIs) oppose the clearance of abnormal intracellular proteins, allowing accumulation to toxic levels particularly in tumor cells.
- PIs are associated with dose dependent **hypertension** from increased **vascular tone**, reactivity, and dysfunction via **endothelial injury** from proteosome inhibition.
- PI dosing should be **modified in uncontrolled hypertension** and **discontinued in hypertensive crises**.
- **TMA** has also been reported as definitively associated with PIs in multiple myeloma patients, more often with **carfilzomib** compared with bortezomib or ixazomib.
- Treatment data are limited, but **drug discontinuation has been necessary**, and use of plasma exchange has been ineffective for PI-associated TMA.

# Immunotherapies

## Immune Checkpoint Inhibitors

- ICIs are mAbs directed **against negative regulatory receptor checkpoints of T-cell immunity**, including
- cytotoxic Tlymphocyte–associated antigen 4 **(CTLA-4) such as ipilimumab**,
- programmed death-1 (PD-1) and PD-1 ligand (PD-L1) pathway [PD-L1]) such as **cemiplimab, nivolumab, pembrolizumab (PD-1)**,
- **atezolizumab, avelumab, and durvalumab (PD-L1**), which prevent T-cell activation.
- ICIs activate dormant antitumor immunity, allowing improved survival in previously **difficult-to-treat malignancies** such as **lung cancer**, **RCC**, and **melanoma**.
- .

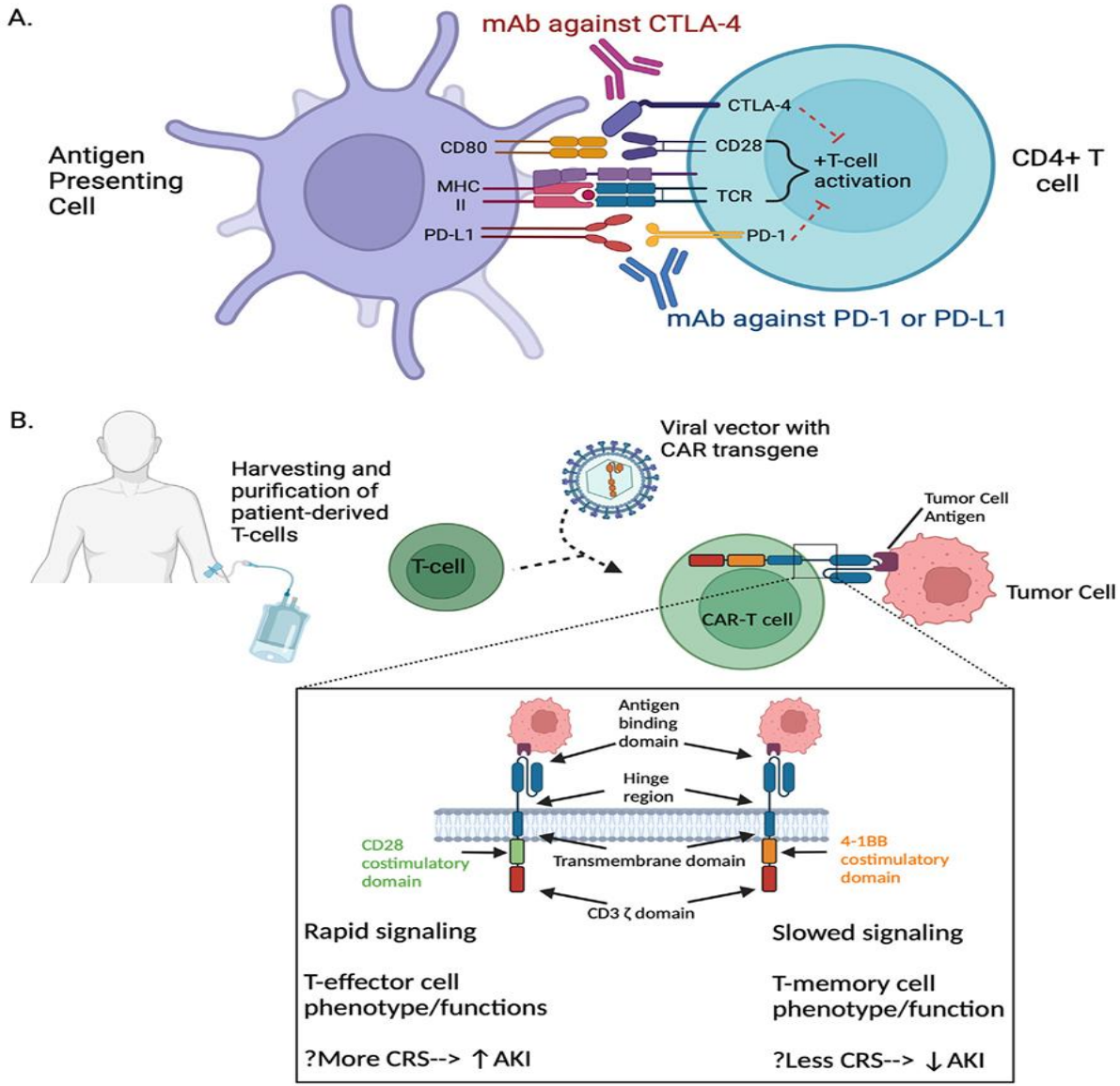



**Figure 2.** The design and rationale of immunotherapy. (A) T cells are normally activated by 2 signals. (1) Antigen presenting cell displaying an antigen in the context of a self-MHC molecule to a T cell with receptor specificity for that antigen. (2) Binding of a costimulatory molecule (eg, CD28) on the T cell to its cognate ligand on the antigen presenting cell (eg, CD80/CD86). Negative regulatory checkpoints such as CTLA-4 or PD-1 on the T cell interfere with costimulation or bind to PD-L1, respectively, to inactivate T cells. Monoclonal antibodies against PD-1 and CTLA-4 prevent T-cell anergy against tumor cell antigen by preventing the inactivation of T cells. (B) CAR-T production begins with harvesting of T cells from the patient who is a candidate for CAR-T therapy. These

- ICIs are associated with off-target **immune-related adverse** events (IRAEs), commonly involving the **skin**, **endocrine system**, and **gastrointestinal tract**.
- Although the kidney is less involved, **nephrotoxicity** occurs in up to **2% to 5%,** with a higher risk with combination ICIs.
- Risk factors for ICI-AKI include use of **PPIs and NSAIDs**.

- AKI is the most common kidney IRAE from ICIs, and **AIN** is the most reported histopathologic finding.
- Glomerular diseases such as **MCD, FSGS, MN, lupus nephritis** have also been described, as have electrolyte derangements including distal renal tubular acidosis.

- ICI-AKI warrants drug suspension pending workup of AKI.
- In either suspected or confirmed AIN, **corticosteroid dosing at 12 mg/kg** allows recovery from ICI-AIN.
- **Biopsy** should be considered for patients whose AKI **does not respond to such dosing**.
- The optimal dose and duration of corticosteroids for ICI-AIN is unclear though observational data have suggested that shorter-term (w1 month), tapered dosing may be reasonable if AKI recovery is sustained after taper.
- Recent retrospective data from >400 patients have shown a **recurrent ICI-AIN rate of 16.5%.**

# Chimeric Antigen Receptor T Cells

- Chimeric antigen receptor T-cells (CAR-T) are **patient derived T cells** modified ex vivo to **express a chimeric receptor** with an external **tumor antigen** domain allowing direct CAR-T activation via linked costimulation and CD3 ζ chain domains.
- Upon infusion, **CAR-T recognize tumor antigens and become activated to release of proinflammatory cytokines, particularly interleukin 6 (IL-6).**

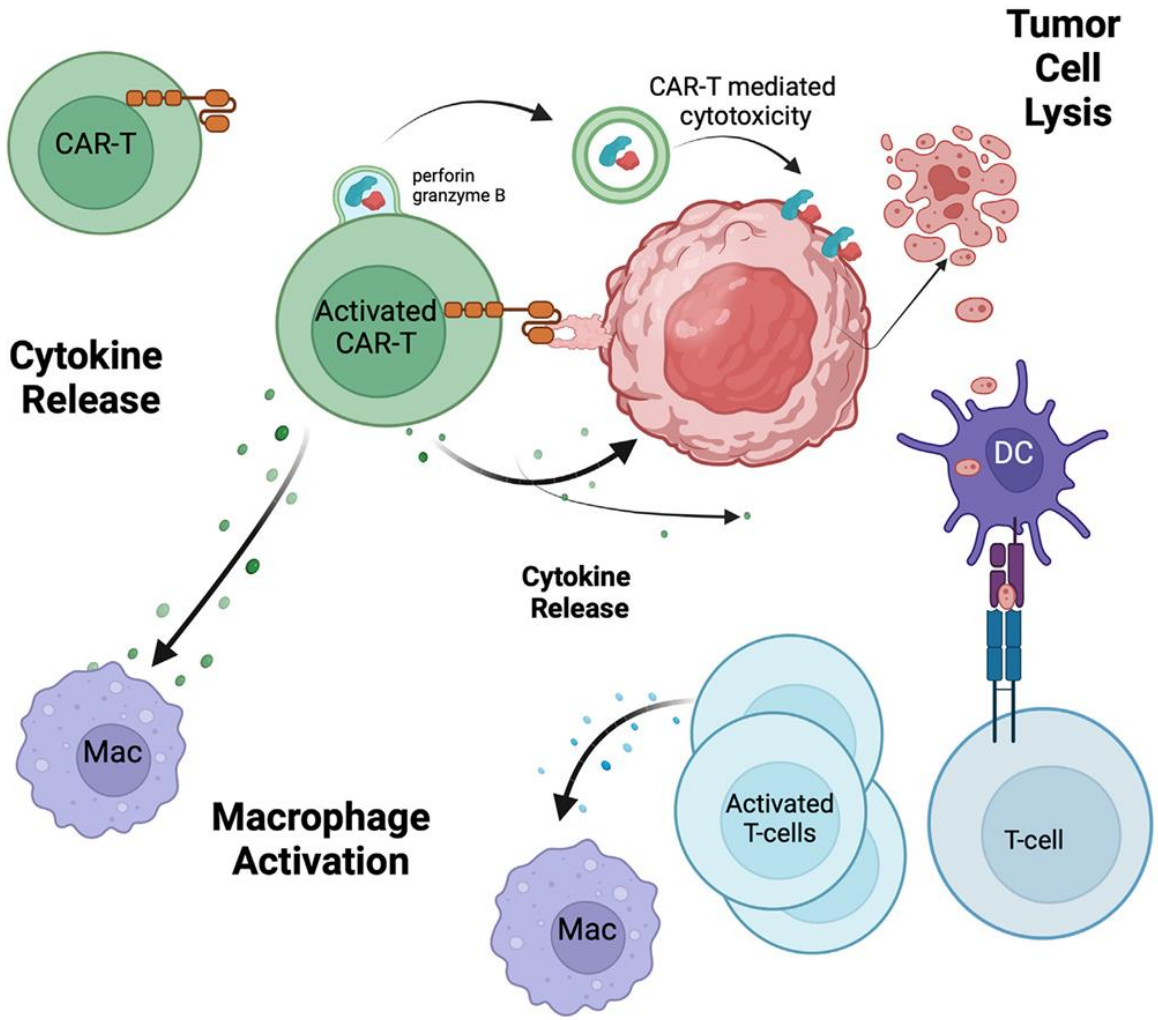



**Figure 3.** A schema of the various inflammatory responses with CAR-T. Recognition of tumor specific antigen activates CAR-T effector mechanisms aimed at tumor control including cytokine release, tumor lysis, and macrophage activation. These mechanisms may occur simultaneously or independently of each other. Cytokines released by CAR-T include IL-2, which allows expansion of CAR-T cells in vivo, while IL-6 and IFN-γ have tumoricidal properties. Additional cytotoxicity of CAR-T is mediated by perforin/granzyme B. Depending on the scale of tumor cell death, tumor lysis syndrome may result. Tumor cell death also releases novel antigen that if processed by antigen-presenting cells such as DCs and macrophages can activate native T cells. Activated T cells have their own effector mechanism of cytokine release. Thus, multiple pathways can converge to result in cytokine release syndrome, a large, systemic inflammatory cascade that is characterized by fever, hypotension, and other manifestations of severe inflammation. Created with Biorender.com. Abbreviations: CAR-T, chimeric antigen receptor T-cells; DC, dendritic cells; IFN-γ, interferon γ; IL, interleukin; MAC, macrophages; and TLS, tumor lysis syndrome.

- **Cytokine-release syndrome (CRS)** is clinically characterized by **fever, hypotension, diarrhea,** and potential for **IL-6-driven severe neurotoxicity**.
- **Hemodynamic shifts may result in AKI** on the prerenal to **ATN** spectrum, though **tumor lysis** and macrophage activation syndromes have also been described .
- Retrospective data report **AKI rates** of **5% to 30%** with CAR-T, which correlates with the incidence of CRS.
- This wide range of AKI is likely related to the type of costimulatory domain, as **CD28 is thought to have more potent CAR-T activation** and **CRS.**

- CRS management, which often includes intensive care monitoring, includes **corticosteroids** and IL-6 receptor blockade (**tocilizumab**), especially for patients with CRS related **neurotoxicity**.

# Nephrotoxicity of Other Therapies Used in Anticancer Management

- Bisphosphonates
- Used to counteract up-regulated osteoclasts, high-dose intravenous bisphosphonates have been associated with **cumulative**, **dose-dependent** **FSGS (pamidronate)** and **ATN (zoledronate)**.
- Dosing is not recommended for most of these agents for **CLcr < 30** mL/min, though the **benefits may outweigh** the risks with short-term **pamidronate use**.
- **Reducing cumulative doses** and **increasing dose intervals** may prevent bisphosphonate nephrotoxicity.

# Mammalian Target of Rapamycin Inhibitors

- Everolimus and sirolimus are used in various malignancies, including **RCC**, **breast, neuroendocrine tumors**, and **angiomyolipomas**.
- **Proteinuria** has been reported in **3% to 36%** of patients on everolimus and sirolimus.
- Kidney biopsies of patients with mammalian target of rapamycin (mTOR) inhibitor induced proteinuria have displayed **FSGS**.
- Proteinuria induced by an mTOR inhibitor is **treated with RAAS** inhibitors, but **nephrotic range proteinuria requires drug discontinuation**.

# Calcineurin Inhibitors

- Calcineurin inhibitors (CNIs) are used as immunosuppressants with certain glomerular diseases, with **solid organ transplantation**, and as **prophylaxis against graft versus-host disease (GVHD)** for **allogeneic** hematopoietic stem cell transplantation (**SCT**).
- CNIs cause **afferent arteriolar vasoconstriction**, which if prolonged can cause **ischemic ATN**.
- Toxic ATN also has been described, resulting in characteristic vacuolization of tubular cell cytoplasm.
- CNIs are infrequently associated with **systemic or kidney-limited TMA**.
- CNIs may cause **magnesium wasting** in the kidney, which mechanistically occurs via TRPM6 down-regulation.

# Electrolyte and Acid-Base Disorders in Cancer

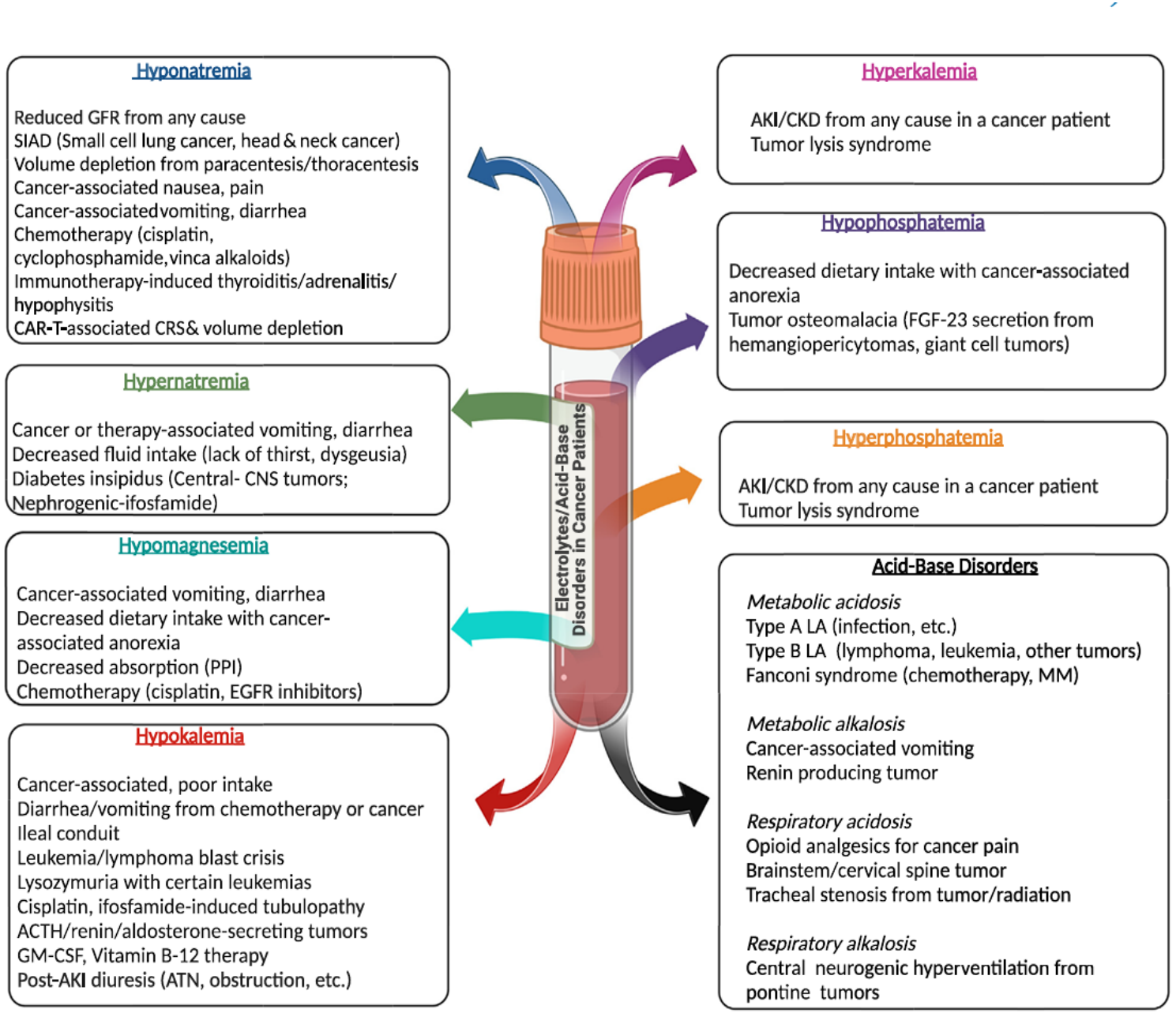



**Figure 4.** Electrolyte and acid-base disorders in patients with cancer, including hyponatremia, hypernatremia, hyperkalemia, hypoka-

# Kidney Injury in Hematologic Malignancies

- The kidney is a target for end-organ injury in patients with hematological cancers, either directly due to the **malignancy** or indirectly via **its treatment**.
- kidney injury associated with
- **tumor lysis syndrome**,
- **monoclonal gammopathy-related kidney disease**,
- **leukemia/lymphoma.**

**Table 3.** Cairo-Bishop Definitions for Tumor Lysis Syndrome, Along With Grading by Severity of End-Organ Complications

| Laboratory TLS: ≥2 or More Derangements 3 Days Before or 7 Days After Chemotherapy | | |
|---|---|---|
| **Electrolyte/Metabolic-Breakdown Product** | **Absolute Value** | **Percent Change From Baseline** |
| Calcium | <7.0 mg/dL | Decrease of at least 25% |
| Phosphorus | >4.5 mg/dL (adults), >6.5 mg/dL (children) | Increase of at least 25% |
| Potassium | >6 mEq/L | Increase of at least 25% |
| Uric acid | >8.0 mg/dL | Increase of at least 25% |

| Clinical TLS: Laboratory TLS *and* ≥1 Clinical Complication | | | | | | |
|---|---|---|---|---|---|---|
| **End-Organ Complication** | **Grade of Organ Injury** | | | | | |
| | **0** | **1** | **2** | **3** | **4** | **5** |
| Cardiac arrhythmia *or* sudden death | None | No indication for intervention | Only nonurgent medical intervention | Incomplete control with medication or use of AICD | Severe life-threatening arrhythmia (syncope, heart failure, etc) | Death |
| Serum creatinine | <1.5 × ULN | 1.5 × ULN | >1.5-3 × ULN | >3-6 × ULN | >6 × ULN | Death |
| Seizures | None | Not defined | One brief generalized seizure controlled with AEDs or infrequent focal motor seizures | Seizures with altered consciousness, breakthrough generalized seizures | Prolonged, repetitive or difficult to control (status epilepticus, refractory to meds) | Death |

Based on information in Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3-11. https://doi.org/10.1111/j.1365-2141.2004.05094.x. Abbreviations: AEDs, antiepileptic drugs; AICD, automated implantable defibrillator; TLS, tumor lysis syndrome; ULN, upper limit of normal.

- TLS results when purine nucleotides released from dying tumor cells are converted to xanthine and uric acid by xanthine oxidase.
- Acidic conditions favor **uric acid precipitation** in the PTEC lumen, causing ATN from **direct injury** and **inflammatory pathways**.
- Cell death also releases electrolytes, leading to **hyperkalemia** and **hyperphosphatemia.**
- Phosphorus complexes with calcium, causing hypocalcemia and **calcium-phosphorus nephrocalcinosis**, the latter also contributing to AKI.

- Prophylactic **allopurinol** and **febuxostat prevent** further rises in baseline uric acid levels.
- This does not treat existing hyperuricemia, and high-level xanthine accumulation may result, which is also potentially nephrotoxic.
- **Allopurinol requires GFR dose adjustment**, and h**ypersensitivity** has been noted.
- **Febuxostat's cost** and availability have limited its use.
- **Recombinant rasburicase** cleaves **uric acid** to the **soluble allantoin** and is used **prophylactically in high-risk TLS patients**.
- It effectively **lowers pre-existing high uric acid levels** but is **contraindicated** in patients with **glucose6-phosphate dehydrogenase deficiency**.
- Finally, uric acid excretion with **saline diuresis to target urine output ≥ 2 mL/kg/h** is standard practice.
- **Urine alkalinization should be avoided** because it worsens calcium-phosphate precipitation.

# Monoclonal-Gammopathy-Related Kidney Disease

## Amyloidosis (AL, AH, AHL)

NS, subacute kidney injury, CKD, extra-renal disease common. AL>AHL, AH rare

+M-prot in most

Biopsy:
LM: Congo red deposits in mesangium, CW

IF:κ or λ LC restricted staining

EM: Randomly arranged 9-11nm fibrils

## C3 Glomerulopathy

Hematuria, Proteinuria, NS, subcute AKI

+M-prot in most, ↓C3

Biopsy:
LM: mesangial, endocapillary, or MPGN

IF: Granular C3 in GBM/ mesangium. No Ig deposits likely w/o protease degradation

EM: glomerular deposits

## MIDD (LCDD, HCDD, LCHDD)

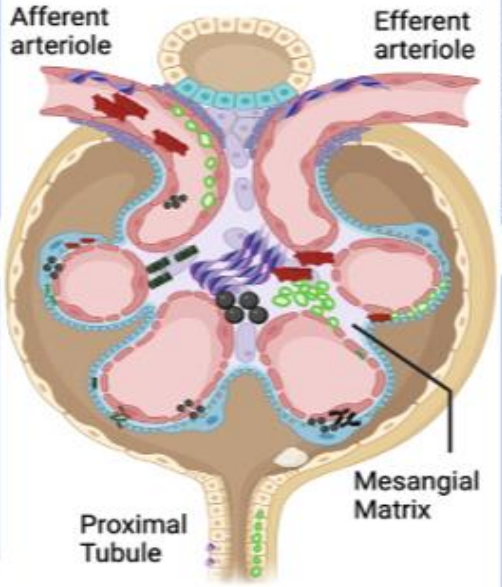
Sub-nephrotic proteinuria, NS, reduced GFR, extra-renal disease less common than amyloid

+M-prot, but MGRS rates>MM

Biopsy:
LM: Nodular mesangial sclerosis, Thick TBM.

IF: LCDD/LCHDD-glomerular/TBM κ or λ staining ; HCDD-C3, HC staining

EM: EDD with punctate/ground pepper appearance in glomerular and TBMs and vessels.




## LC proximal tubulopathy

Proteinuria, slowly progressive kidney disease

Detectable M-prot in most patients

Biopsy:
LM: proximal tubular swelling +/- inclusions

IF: proximal tubular staining for k (crystalline) tubulopathy or λ (non-crystalline tubulopathy);

EM: proximal tubular LC crystals or lysosomal inclusions

## Monoclonal Type I Cryoglobulinemia

Hematuria, Proteinuria, NS, AKI, HTN, low C4

+M-prot, most with MGUS/MM/ lymphoproliferative disorder

Biopsy:
LM:MPGN, MSGN ,ECGN, crescentic GN

IF:granular Ig deposits in mesangium, CW, vessel walls

EM: SUE, mesangial EDD +/- substructure (fibrillar, tubular, tactoid)

## PGNMID

Hematuria, high-grade proteinuria +/- NS, CKD and HTN.

M-prot and IFE usually negative

Biopsy:
LM: membranous, endocapillary, or MPGN

IF: Granular IgG3κ or IgG1κ in GBM/ mesangium. C3 deposits.

EM: mesangial, SUE deposits

## Immunotactoid glomerulopathy

Proteinuria, NS, CKD, HTN, ↓C3, C4

M-protein and clone in 50-60% of patients

Biopsy:
LM: MPGN, MGN, ECGN, membranous

IF: Clonal IgG deposits in mesangium, SUP; granular deposits in GBM in membranous

EM: parallel microtubules 14-60 nm

# Lymphomatous and Leukemic Kidney Disease

- Kidney disease in patients with leukemias and lymphomas may be clinically silent or present with **proteinuria** and/or **AKI**.
- **Leukemic or lymphomatous kidney infiltration** is usually asymptomatic, but **bilateral interstitial involvement** that increases interstitial pressure may cause AKI via **compressive tubular injury.**
- Flank pain and hematuria are among the signs and symptoms.
- **Glomerular infiltration** more commonly results in **isolated proteinuria** versus AKI.
- Kidney ultrasound in patients with infiltrating leukemia/lymphomas classically shows symmetric kidney enlargement.
- **Metabolic uptake** in the kidney on **positron emission tomography-CT scan** may be seen..

# Paraneoplastic glomerular diseases

- Several **paraneoplastic glomerular lesions** have been noted with different lymphomas/leukemias.
- Most common among these are **MCD** and **FSGS**, which have been described in **Hodgkin lymphoma**, **acute lymphoblastic leukemia**, **chronic lymphocytic leukemia** (CLL), and **acute and chronic myeloid leukemias**, among others.
- **CLL** also has associations with **MCD/FSGS**, **MN**, and **MPGN**.
- Leukemias with white blood cell counts **> 100,000/mm3** may rarely leadto **intravascular leukostasis** causing **ATN from microvascular** ischemia.

- Unique to **monocytic leukemias**, particularly chronic myelomonocytic leukemia (CMML), **lysozyme nephropathy** is another type of kidney injury associated with hematological malignancies.
- Lysozyme undergoes glomerular filtration and **reabsorption by the proximal** tubule.
- CMML and other leukemias **excessively produce lysozyme** which is directly toxic to proximal tubule cells with supraphysiological reabsorption.
- **SPEP may show a gamma-region spike**, but immunofixation electrophoresis (**IFE)** will be **negative for a monoclonal component**.
- Clinically, patients experience **AKI from ATN** as well as **nonalbumin proteinuria** from lysozyme excretion into urine. **Hypokalemia** may also be present.
- Light microscopy typically reveals ATN with **hypereosinophilic granules within the PTEC cytoplasm that stain positive for lysozyme** on immunohistochemistry.
- Electron microscopy shows numerous auto-phagolysosomes.

# Kidney Disease Associated With Hematopoietic StemCell Transplantation

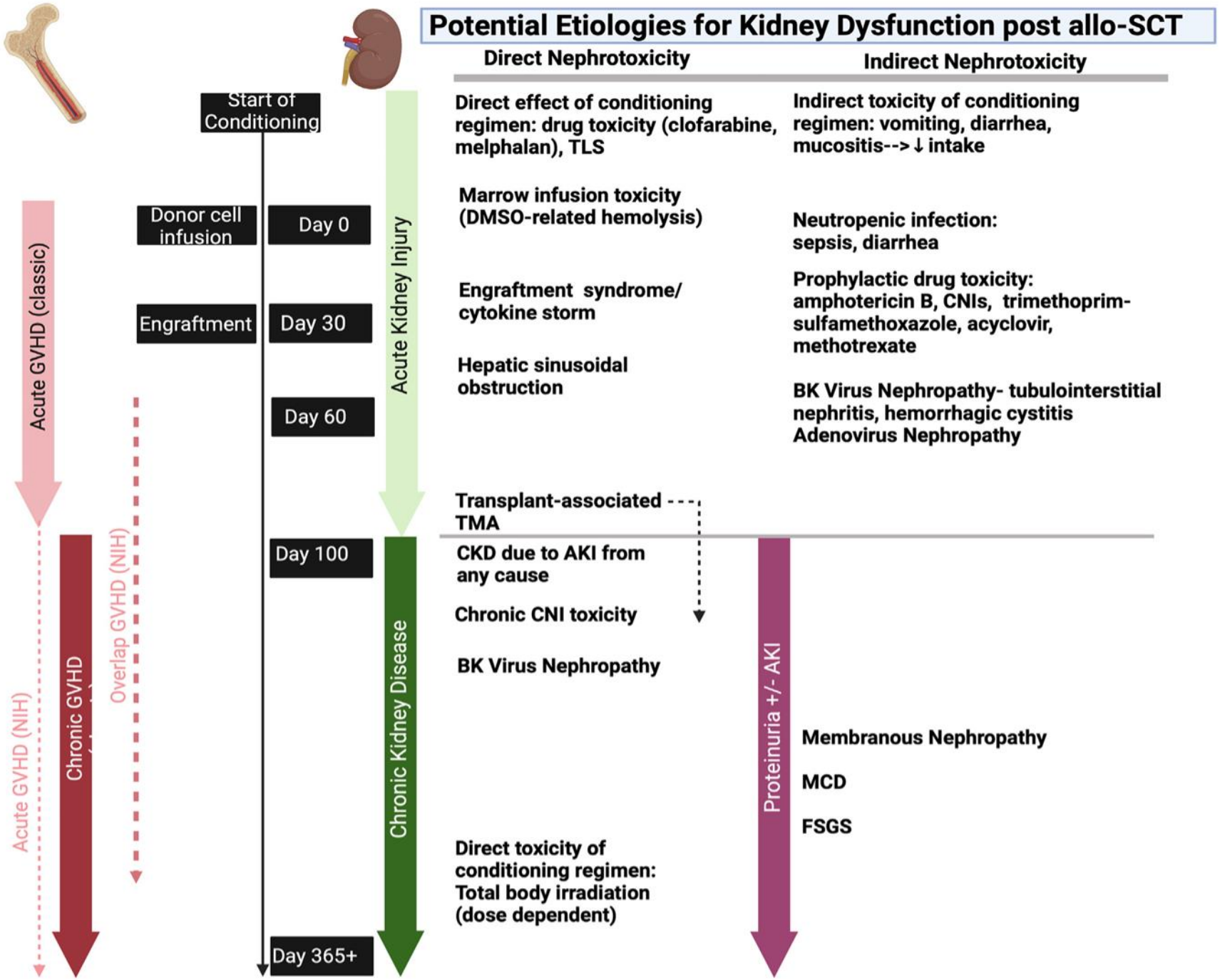
- Hematopoietic SCT is curative-intent therapy for both malignant and non-malignant hematological and nonhematological diseases.
- In **autologous SCT**, the patient self-donates stemcells; in allogeneic SCT, related/unrelated donors provide cells.
- **Allogeneic SCT** requires **GVHD prophylaxis**.
- Conditioning may be **myeloablative** for cancer **and bone marrow eradication** or **nonmyeloablative with sufficient immunosuppression** to allow engraftment.
- Depending on the **type of SCT,** patients may experience kidney disease due to **bone marrow conditioning** treatments in the pretransplant phase, **prophylactic drugs** after transplant, or **direct effects of the transplant itself**.

- SCT patients are susceptible to **indirect** and **direct** nephrotoxicity of **myeloablative conditioning** regimens.
- These treatments are associated with **mucositis**,**vomiting**, and **diarrhea**, all of which may lead to **volume depletion** and **AKI** along the prerenal/ATNspectrum.
- **Clofarabine** and melphalan used in such regimens have been linked to **direct tubular toxicity**, though biopsy data are sparse and confounding risk factors for AKI exist in the post-SCT period.

- AKI features prominently in engraftment syndrome, a constellation of rash, fever,pulmonary edema, and other symptoms that is typically seen within 7-10daysofSCT.
- SOS presents with abdominal pain, jaundice,and elevated liver enzymes from hepatic sinusoidal injury, which if prolonged results in portal hypertension.
- AKI with SOS is similar to hepatorenal syndrome.

- GVHD represents immune-mediated organ injury by donor cells.
- The classic definitionof aGVHD/cGVHD is timebased;however,updated consensus criteria  are both time and symptom based.
- Kidney biopsies in suspected kidney-GVHD have shown infiltrating tubulointerstitial T cells.
- Patients with kidney-GVHD may present with AKI with or without proteinuria as well isolated proteinuria.
- MN inSCT can be amanifestation of chronic GVHD.
- Reported target antigens include PLA2 R,NELL-1, andFAT1. MCD and FSGS have also been described.

- TA-TMA is similar in clinical presentation toTMA in the non-SCTsetting,with reported incidence rates of 8.2% to 39.0%.
- Management of AKI and CKD after SCT is tailored to the etiology of AKI.
- For example, GVHD requires increased immunosuppression whereas TMA may require holding CNIs out of concern for drug-induced TMA.
- Defibrotide is approved in the UnitedStates for treatment of SOS.
- The patient in case 6 m eets thecriteria forTMA with microangiopathic hemolytic anemia, thrombocytopenia,and proteinuric AKI.
- Busulfan is a risk factor for TA TMA but is not thought to be the primary driver forTMA after transplant.
- The patient is not exhibiting skin changes consistent with skin cGVHD.
- Post engraftment syndrome is an inflammatory reaction that occurs in the immediate post-transplant period as neutrophils recover.
- He likely has TA-TMA, particularly given the multiple risk factors, including GVHD,CNIuse, and myeloablative conditioning, meaning that answer (b) is the best response to question6.


Potential Etiologies for Kidney Dysfunction post allo-SCT
Direct Nephrotoxicity
Indirect Nephrotoxicity
Start of Conditioning
Donor cell infusion
Day 0
Engraftment
Day 30
Day 60
Day 100
Day 365+
Acute GVHD (classic)
Acute GVHD (NIH)
Chronic GVHD
Overlap GVHD (NIH)
Acute Kidney Injury
Chronic Kidney Disease
Proteinuria +/- AKI
Direct effect of conditioning regimen: drug toxicity (clofarabine, melphalan), TLS
Indirect toxicity of conditioning regimen: vomiting, diarrhea, mucositis--> ↓ intake
Marrow infusion toxicity (DMSO-related hemolysis)
Neutropenic infection: sepsis, diarrhea
Engraftment syndrome/ cytokine storm
Prophylactic drug toxicity: amphotericin B, CNIs, trimethoprim-sulfamethoxazole, acyclovir, methotrexate
Hepatic sinusoidal obstruction
BK Virus Nephropathy- tubulointerstitial nephritis, hemorrhagic cystitis Adenovirus Nephropathy
Transplant-associated TMA
CKD due to AKI from any cause
Chronic CNI toxicity
BK Virus Nephropathy
Membranous Nephropathy
MCD
FSGS
Direct toxicity of conditioning regimen: Total body irradiation (dose dependent)

# Cancer in Kidney Transplant Recipients

- Patients with **CKD** and/or **end-state renal disease** have a heightened **cancer risk** that is thought to **reflect uremic immune dysfunction**.
- In kidney transplant recipients (KTRs), improved GFR may restore that dysfunction, but **posttransplant immunosuppressants** abrogate that advantage.

- **Cancer** is the **second-leading cause of death** in KTRs.
- Compared with the general population, KTRs have a **2- to 3-fold higher** cancer risk,.
- Standardized **incidence ratios** in KTRs are **highest for Kaposi** sarcoma, non-melanoma **skin cancers**, **RCC**, and (**PTLD**).
- The standardized **mortality ratios are highest** for **PTLD**, **RCC,** and **melanoma**.
- Given this, **annual dermatological screening** is minimal standard for all KTRs.
-

- **Cystic** kidneys because RCCs in KTRs are more common in **native** kidneys.
- **PTLD** in KTRs is rare, but the **mortality risk approaches 50%.**
- **Most PTLD is associated with Epstein-Barr virus (EBV**), and opinion-based recommendations **suggest viral load monitoring for EBV higher-risk** KTRs (recipient EBV-seronegative, donor EBV-seropositive).

- **Cancer diagnoses** in KTRs require **complex decision making** because
- (1) **anticancer therapy** has the same **potential for nephrotoxicity** in native versus allograft kidneys and
- (2) **maintenance immunosuppression** sustains transplant tolerance but **opposes tumor regression.**
- This requires collaboration between oncologists and transplant nephrologists to individualize cancer treatment **based on residual kidney allograft function** and **patient goals**.
- A consideration for KTRs is use of **ICIs,** which carries **acute rejection rates of w40% in** multiple studies.
- Concurrent use of **mTOR inhibitors may reduce this rejection risk** while maintaining antitumor efficacy, but studies are pending.

- Although mTOR inhibitors do have **antineoplastic activity** and **may reduce relapse rates in SCC** patients, there is concern that mTOR inhibitors carry **a higher mortality risk in KTRs**.

Thank you for your attention

# Biomarkers in CKD

# Biomarkers in CKD Patients

**TABLE 1** | Tumor markers in CKD.

| Tumor markers | CKD | | Significance | References |
|---|---|---|---|---|
| | Non-dialysis | On dialysis | | |
| CEA | H | H | Monitoring for malignancy in uremic patients might be unreliable | Tzitzikos et al., 2010; Cases et al., 1991; Rani et al., 2019 |
| SCC | H | H | Monitoring for malignancy in uremic patients might be unreliable | Cases et al., 1991; Xiaofang et al., 2007 |
| CA50 | H | H | Monitoring for malignancy in uremic patients might be unreliable | Cases et al. (1991) |
| NSE | H | H | Monitoring for malignancy in uremic patients might be unreliable | Cases et al., 1991; Xiaofang et al., 2007 |
| CA125 | N or H | N | Monitoring for malignancy in dialysis patients might be unreliable | Cases et al., 1991; Mikkelsen et al., 2017 |
| CA153 | N or H | N or H | Monitoring for malignancy in uremic patients might be controversial | Cases et al., 1991; Xiaofang et al., 2007; Rani et al., 2019; Tzitzikos et al., 2010 |
| CA199 | N or H | N | Monitoring for malignancy in uremic patients might be comparatively reliable | Cases et al., 1991; Xiaofang et al., 2007; Rani et al., 2019; Mikkelsen et al., 2017 |
| CA724 | N | N | Monitoring for malignancy in dialysis patients might be reliable in dialysis patients | Xiaofang et al. (2007) |
| CYFRA21-1 | H | — | Monitoring for malignancy in uremic patients might be possibly unreliable | Xiaofang et al., 2007; Mikkelsen et al., 2017 |
| HCG | H | — | Monitoring for malignancy in uremic patients might be possibly unreliable | Rani et al. (2019) |
| PSA | N | N | Monitoring for malignancy in uremic patients might be possibly reliable | Cases et al. (1991) |
| AFP | N | N | Monitoring for malignancy in uremic patients might be reliable | Tzitzikos et al., 2010; Cases et al., 1991; Xiaofang et al., 2007 |
| PAP | N | N | Monitoring for malignancy in uremic patients might be possibly reliable | Cases et al. (1991) |
| CGA | H | — | Monitoring for malignancy in uremic patients might be possibly unreliable | Mikkelsen et al. (2017) |

*H = high serum level; N = normal serum level.*

- Rani et el have shown that in advanced CKD patients(stages G4 and G5) without tumor the levels of CEA, HCG,CA199, andCA 153significantly higher compared to the healthy controls.

- It was illustrated that CA153 and CA125 elevated in CKD patients without tumorigenesis but might be associated with concomitant active hepatitis C.

- Nevertheless, there were studies indicating that serum levels of cytokeratin19 fragment (**CYFRA21-1**) might be involved in the development of **epithelial cell carcinoma** and chromogranin A **(CGA**) be associated with **neuroendocrine tumor** in CKD patients, and their reference limits might differ from those of healthy subjects.

- Another study found that **CEA**, squamous cell carcinoma (**SCC)**, carbohydrate antigen 50 (**CA50**) and neuron-specific enolase (NSE)
- showed high false positive rates compared to normal reference values
- of the indicators in CRF patients and concluded that these values were unreliable.

- CRF patients, whereas carbohydrate antigen 125 (**CA125**), **CA153**,
- CA199, alpha-fetoprotein (**AFP**), prostate-specific antigen (**PSA**)
- and prostatic acid phosphatase (**PAP**) were still specific for
- assessing tumors in CRF with **different cutoff values**.

- And a recent study mentioned that prostate-specificantigen (**PSA**), alpha-fetoprotein (**AFP)**, and β-human chorionicgonadotropin (**β-HCG**) might be reliable for cancer screening indialysis patients, while total prostate-specific antigen (TPSA) and β2-microglobulin (β2-M) might be of some value in patients after renal transplantation.

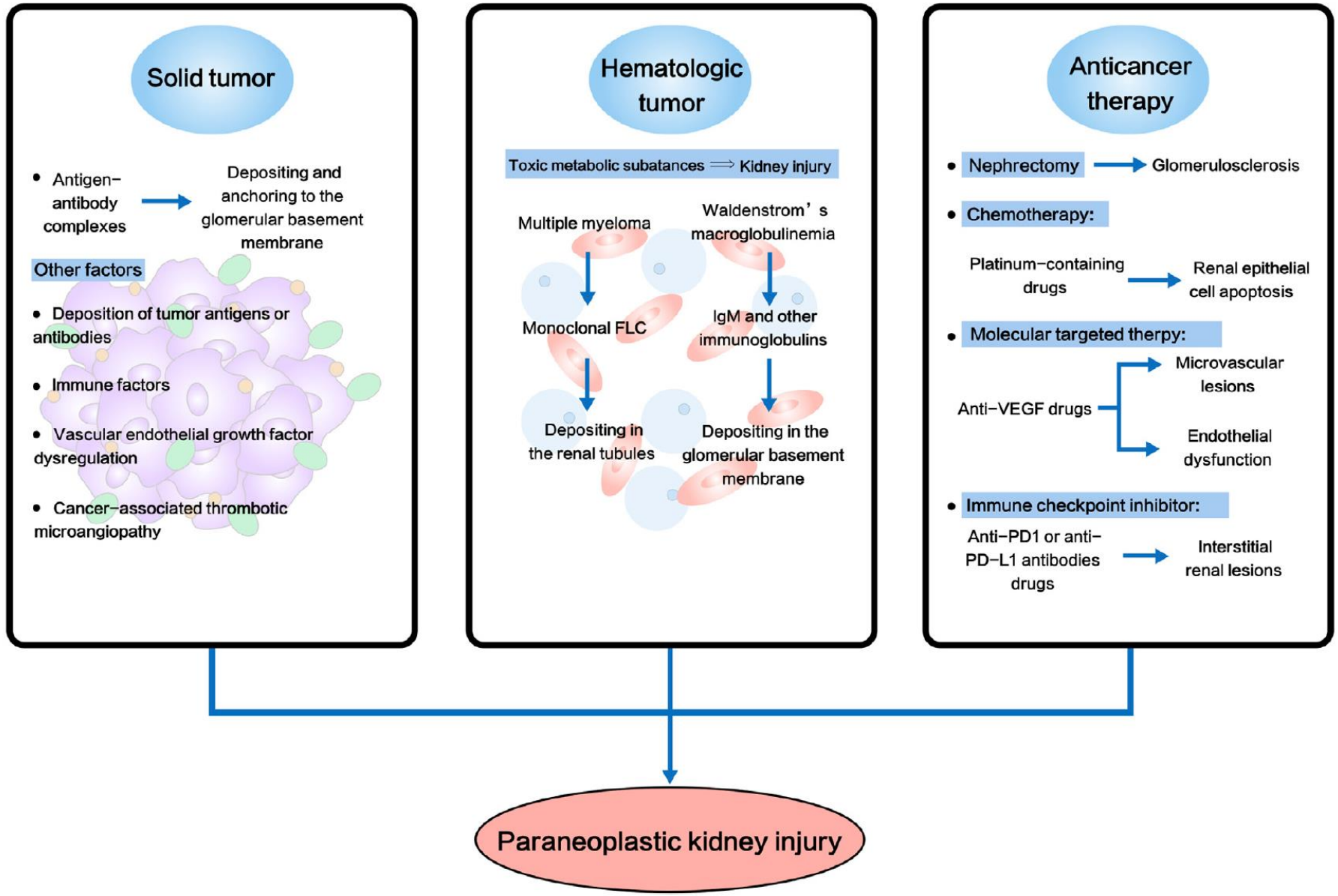



**FIGURE 2 |** Schematic diagram of potential molecular mechanisms of paraneoplastic kidney injury. Paraneoplastic kidney injury was linked to solid tumor, hematologic malignancies and anti-cancer therapies. FLC, free light chain; VEGF, vascular endothelial growth factor; PD1, programmed death 1; PD-L1, programmed death ligand-1.