Challenging but helpful nephrology consults in the oncology ward

Jolanta Malyszko

Department of Nephrology, Dialysis and Internal Medicine
Warsaw Medical University,
Poland

- Onco-nephrology is a rapidly growing subspecialty area within nephrology.
- This area of subspecialization combines the unique knowledge and efforts of a number of specialty groups that include nephrologists, oncologists, urologists, intensivists, pharmacologists, and palliative care specialists.

Clinical scenarios

- Patient with prior renal disease in oncology ward
- Patient without prior renal disease in oncology ward experiencing kidney problems
- Imaging studies in oncology settings- CI-AKI
- RCC – clinical problems
- RRT and oncology treatment

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Cancer and the kidney: dangereoux liasons or price paid for the progress in medicine?

Jolanta Małyszko[1], Leszek Kozlowski[2], Klaudia Kozłowska[1], Maciej Małyszko[1] and Jacek Małyszko[3]

[1]2nd Department of Nephrology and Hypertension with Dialysis Unit, Medical University in Bialystok, Poland

[2]Department of Oncological Surgery, Ministry of Interior Affairs, Bialystok, Poland

[3]1st Department of Nephrology and Transplantology with Dialysis Unit, Medical University in Bialystok, Poland

Correspondence to: *Jolanta Małyszko,* ***email:*** *jolmal@poczta.onet.pl*

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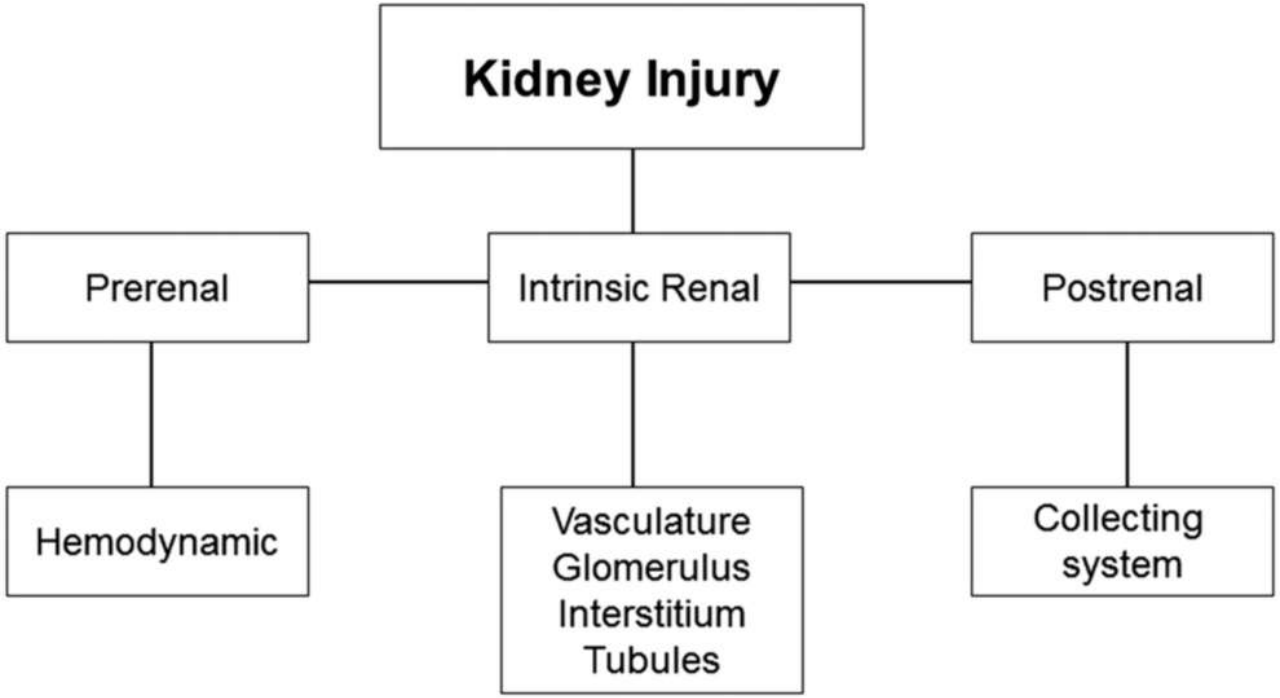
Types of kidney injury



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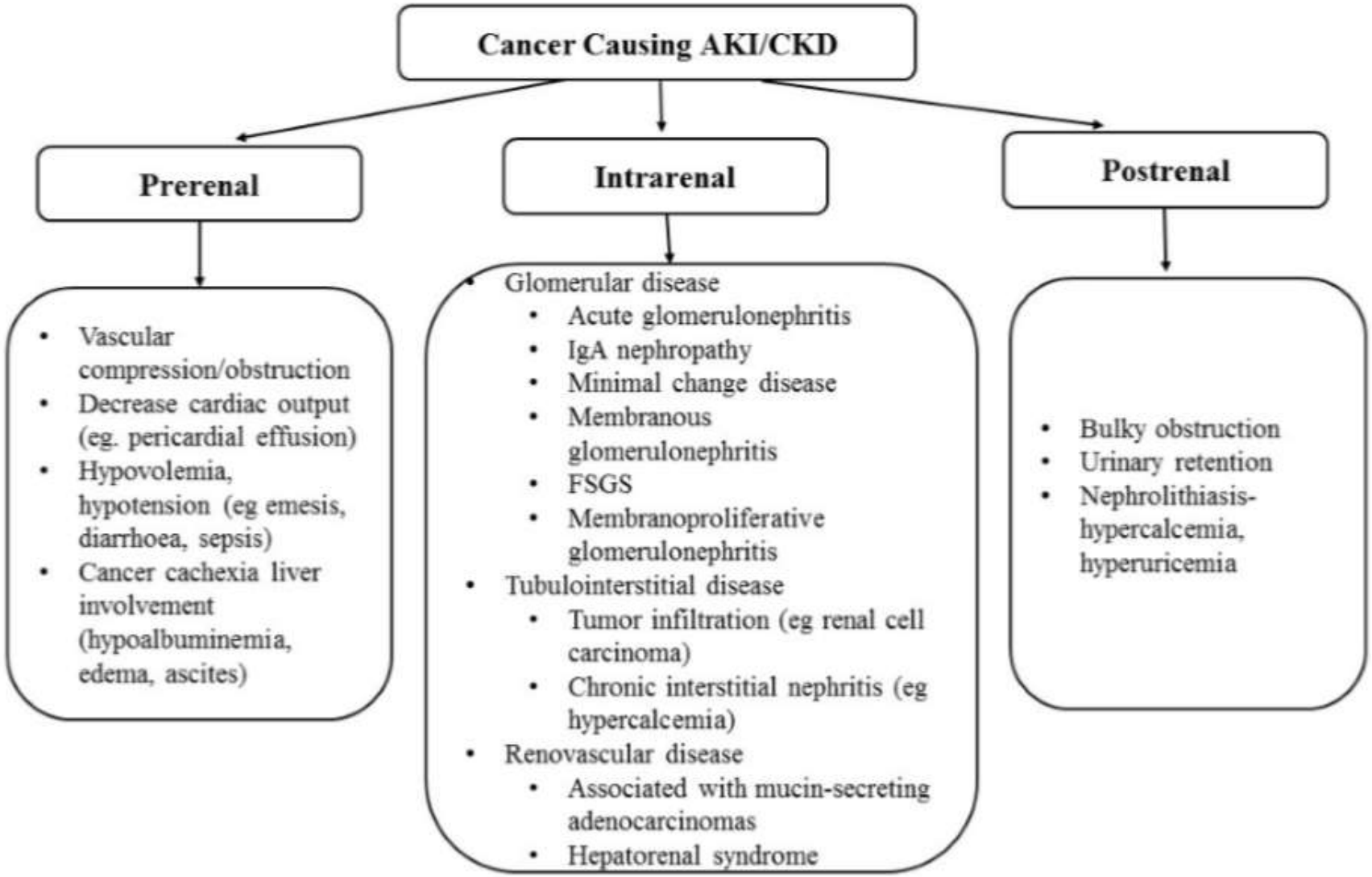


Figure 1: Cancer causing acute kidney injury (AKI) and/or chronic kidney disease (CKD).

Acute kidney injury in patients with malignancy

- AKI and disturbances in electrolyte are the most common feature of kidney disease that are found in a patient with malignancy in a hospital setting.
- AKI in this population is linked with high morbidity and mortality.

- AKI incidence in these vulnerable patients depends upon type of malignancy (solid tumor or hematological malignancy), severity of underlying disease, complications of the disease and therapy.

AKI- Risk factors

- Several factors may potentiate the risk of AKI in these patients such as:
  - dehydration due to vomiting, diarrhea,
  - obstruction of urinary tract,
  - fluid and electrolyte disturbances,
  - contrast agent administration,
  - nonsteroidal antiinflammatory drugs (NSAIDs),
  - nephrotoxic antibiotics,
  - renal toxicity of some chemotherapeutic and targeted drugs

Prerenal AKI

- Prerenal AKI is a common in patients with malignancy .
- AKI may be due to true dehydration, resulting from vomiting, diarrhea or sepsis.
- AKI due to dehydration related to malnutrition associated with anticancer therapy is common.
- In sepsis, impaired perfusion and prerenal AKI may be due to hypotension and vasodilation due to either sepsis or administration of vasoconstrictory drugs, i.e. norepinephrine or vasopressin.
- Prerenal AKI may be also caused by drugs such as diuretics, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors or NSAIDs used for either the cancer or other situations.

Prerenal AKI

- Physicians should be aware of the risks and benefits of continuation of these medications in oncological subjects.
- Prevention of the prerenal AKI is adequate hydration and avoidance or withdrawal of potentially nephrotoxic agents

Postrenal AKI

- Intratubular or extrarenal obstruction are frequent causes of AKI in patients with cancer.
- Conversely, malignancy should be considered in any patient not known to have cancer who presents with bilateral urinary tract obstruction that is not associated with urolithiasis.
- Obstruction could be either intratubular or extrarenal.

Postrenal AKI

- Intratubular obstruction can be caused by uric acid crystals (in tumor lysis syndrome), light chain casts, or crystallization of certain drugs i.e high dose methotrexate.
- Obstruction of the bladder outlet or urether(s) is more frequent in malignancies relative to the general population.
- Extrarenal obstruction can be caused by a wide range of malignancies i.e. bladdder, prostate, uterus and cervix cancers may cause obstruction of the urinary tract and postrenal AKI, and usually indicates metastatic disease.
- Ureteral obstruction due to retroperitoneal fibrosis can be also secondary to malignancy.
- Patients with cancer may also develop urinary tract obstruction that is unrelated to the malignancy (eg, benign prostatic hypertrophy in men).

Postrenal AKI

- The most common clinical presentation is anuria, flank pain, a palpable mass or palpable bladder.
- Urinary sediment is usually bland. In a case of partial obstruction, anuria may not be present.
- However, hyperkalemia with nonanion gap metabolic acidosis may suggest renal tubular acidosis due to obstruction .
- On sonography, hydronephrosis or hydroureter are most common findings.

Postrenal AKI

- However, in a case of obstructive AKI due to retroperitoneal fibrosis, malignancy or its treatment, hydronephrosis or hydroureter may not be present.
- It should be also stressed that radiotherapy of the pelvis or abdomen may also lead to retroperitoneal fibrosis.
- Percutaneous nephrostomy or stenting is performed to relief obstruction of the urinary tract, however, recovery is influenced by the severity and duration of the obstructive AKI.

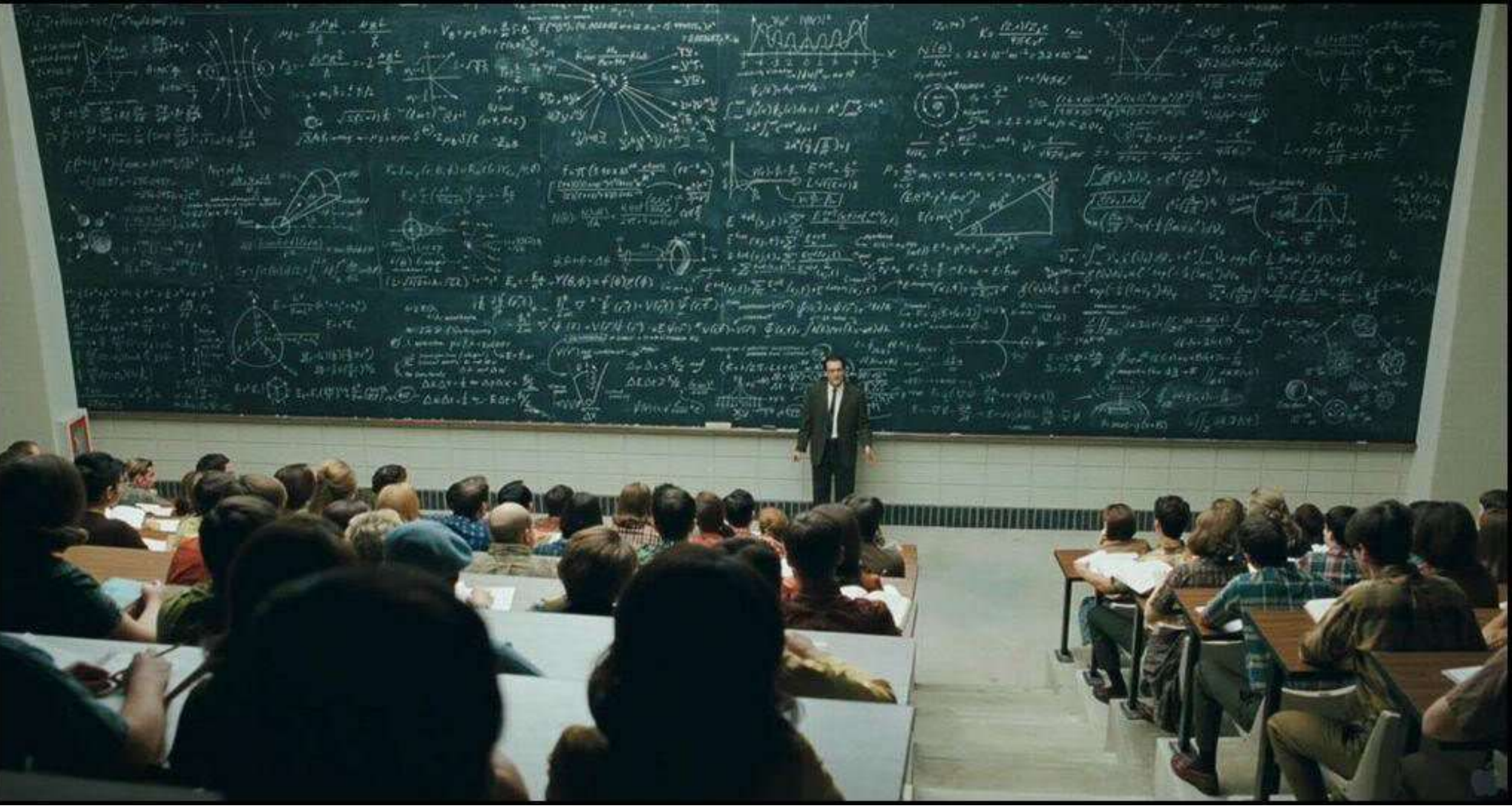
Renal AKI

- Glomerular, tubulointerstitial, and vascular diseases may cause renal function impairment in patients with malignancy.
- In differential diagnosis type of malignancy and type of chemotherapeutic agents are to be considered.
- The most common glomerular pathology in malignancy include vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), membrano-proliferative or membranous glomerulonephritis and thrombotic microangiopathy (TMA) .
- Acute tubular necrosis due to ischemia may be caused by severe dehydration, hypotension or sepsis leading to prerenal AKI and then due to the severity and duration to intrinsic AKI.

Renal function in patients with cancer -problems with estimation

- Creatinine
- eGFR
- Creatinine clearance

- Major issue – cachexia, decreased muscle mass,



And thus, dear students, we have arrived at the formula for understanding women"

CKD in patients with malignancy

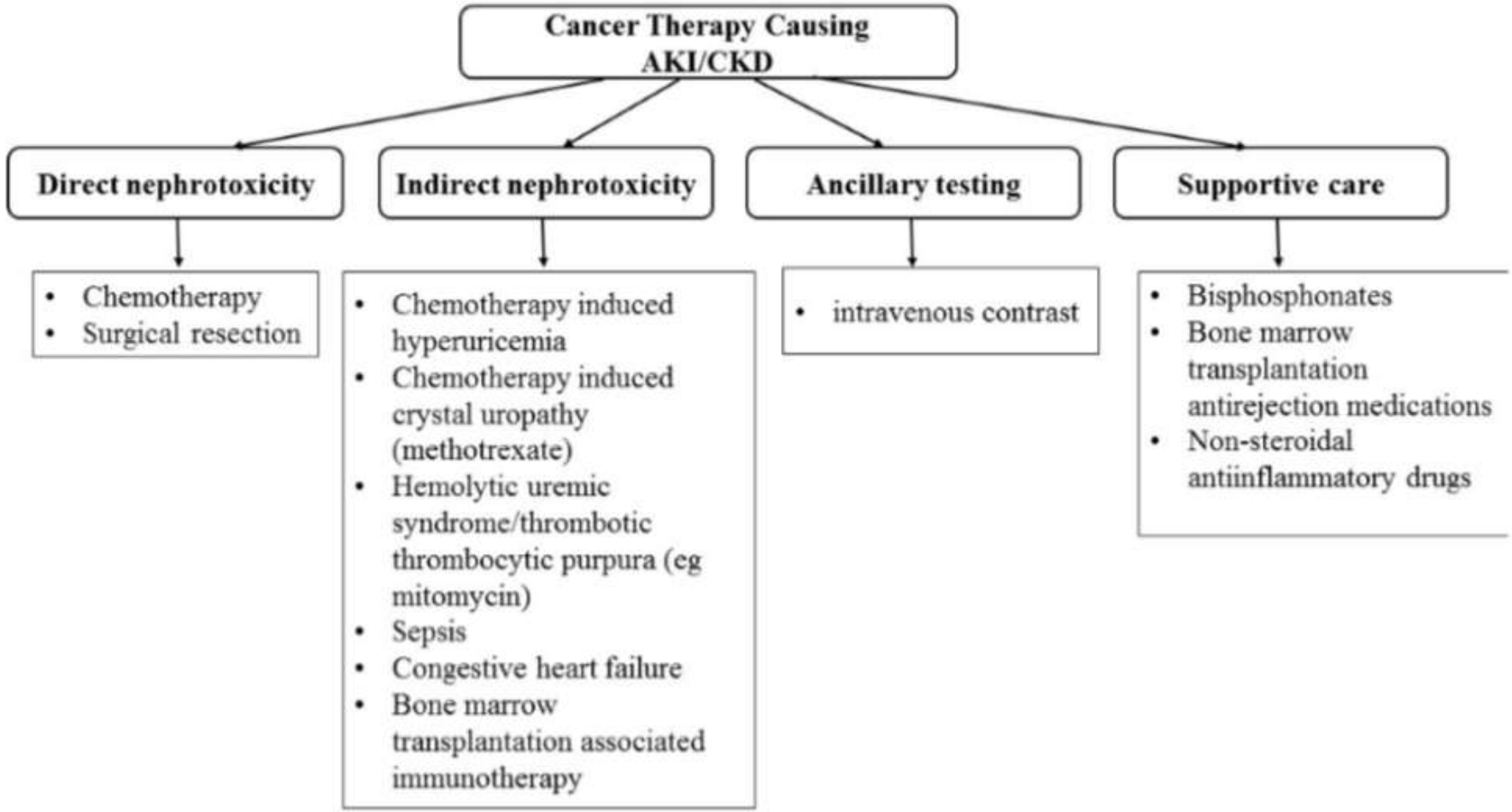


Figure 2: Cancer therapy causing acute kidney injury (AKI) and/or chronic kidney disease (CKD).

Prevalence of CKD in patients with malignancy

- Prevalence CKD is reported to be high in patients with malignancy , but the renal effect of new targeted therapies have not been not widely studied.
- CKD prevalence of ~33 and 27%, respectively, was reported by Dogan et al. and Launay -Vacher et al.
- IRMA-1 (Insuffisance Rénale et Médicaments Anticancéreux; Renal Insufficiency and Anticancer Medications) study included 4684 subjects with malignancy. In this study, 50–60% of the subjects had an abnormal renal function (GFR<90 ml/ min/1.73 m2), whereas SCr was normal in most patients .

Associations between cancer and CKD

- Wong et al. studied a cohort of 3654 subjects and assessed the relation between eGFR and risk of cancer.
- They found that in men, but not in women, with eGFR lower than 55 ml/min/1.73m2, a risk for cancer was significantly higher .
- In particular, lung and urinary tract cancer risk raised by 29% for each 10 mL fall in eGFR (estimated by Modification of Diet in Renal Diseases-MDRD formula).

- Danish registry study assessed the risk for cancer over two 8-year periods of time: 1993– 2000 and 2001–2008.
- The authors found that in the studied periods, the incidence of malignancy per year of risk did not increase significantly, 3.1% versus 2.6%.
- However, the prevalence of cancer rose gradually by 35% from 10.4% in the earlier period to 14.0% in the later period .
- The most common malignancies in this study were skin cancers (basal cell and squamous-cell), breast cancer, cervical cancer, melanoma, followed by colon, respiratory tract, bladder, prostate, and kidney cancers .

- On the basis of these findings, it appears that CKD itself is a risk for cancer, dialyses or kidney transplantation, as reported previously.
- In breast, colorectal, lung, ovarian, and skin cancers, prevalence of CKD was increased
- In addition, breast, cervix, colon, and kidney are more common in CKD than in the general population .

Cancer and renal replacement therapy

- Patients on RRT are dying mainly due to o cardiovascular disease and infections, while malignancy is relatively common in this population.
- About 6% of the incident hemodialyzed subjects in the USA have malignancy as a comorbidity

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Full Review

Nephrotoxicity of anticancer treatment

Jolanta Małyszko[1], Klaudia Kozłowska[1], Leszek Kozłowski[2] and Jacek Małyszko[3]

[1]2nd Department of Nephrology and Hypertension with Dialysis Unit, Medical University in Bialystok, [2]Department of Oncological Surgery, Ministry of Interior Affairs Hospital, Bialystok, Poland and [3]1st Department of Nephrology and Transplantology with Dialysis Unit, Medical University in Bialystok, Białystok, Poland

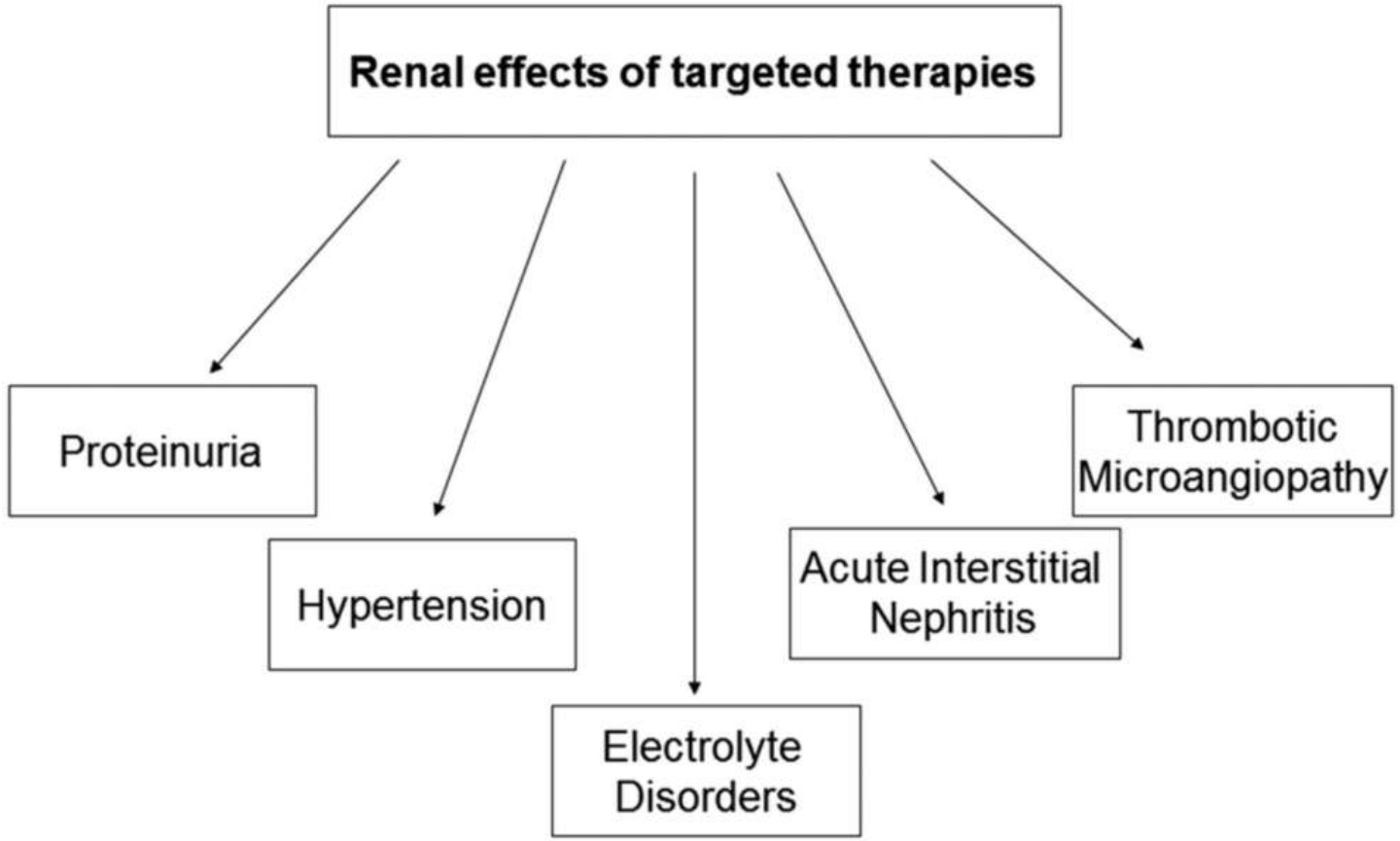
Correspondence and offprint requests to: Jolanta Małyszko; E-mail: jolmal@poczta.onet.pl

Table 1. Anticancer drugs, type of nephrotoxicity, mechanism and prevention of renal adverse events

Medication	Nephrotoxicity	Mechanism of action	Preventive measures
Alkylating agents cyclophosphamide ifosphamide	Hyponatraemia-SIADH haemorrhagic cystitis Fanconi syndrome, renal tubular acidosis, nephrogenic diabetes insipidus	Direct effect on distal tubules proximal tubular damage by acrolein and chloroacetaldehyde	Adequate hydration use of Mesna or N-acetylcysteine electrolyte monitoring
Antitumour antibiotics Mitomycin C	DITMA	Direct endothelial injury	Drug discontinuation, supportive care
Antimetabolites methotrexate pemetrexed gemcitabine clofarabine	AKI non-oliguric (high dose) Hyponatraemia-SIADH AKI, acute tubular necrosis, renal tubular acidosis, diabetes insipidus DITMA AKI	Precipitation of methotrexate and its crystals Decrease in GFR due to arteriolar or mesangial cell constriction	Adequate hydration urine alkalinization, forced diuresis Drug discontinuation, supportive care
Thalidomide and derivatives	AKI, Interstitial nephritis	Crystal nephropathy	Adequate hydration
Vinca alkaloids	Hyponatraemia DITMA	SIADH	
Platinum derivatives	Renal failure, renal tubular acidosis, hypomagnesaemia (dose-related and cumulative) Recurrent salt wasting	Tubular injury	Aggressive hydration Forced diuresis
Proteasome inhibitors	Thrombotic microangiopathy AKI		Drug discontinuation, supportive care
Anti-angiogenesis drugs VEGF pathway inhibitors, TKI	Proteinuria, nephrotic syndrome Hypertension AKI, thrombotic microangiopathy	Anti-VEGF antibodies	
EGFR pathway inhibitors	Hypomagnesaemia	Tubular injury	
BRAF inhibitors	AKI, acute interstitial nephritis acute tubular necrosis, Fanconi syndrome, electrolyte disturbances SIADH	Tubular toxicity	
ALK inhibitors	AKI		Supportive care
Checkpoint inhibitors Anti-PD-1 and PDL-1 therapies Anti-CTLA-4 antibody	Acute interstitial nephritis Acute interstitial nephritis, AKI, acute tubular necrosis, acute tubular injury, nephrotic syndrome	Suppression of T-cell immunity cell-mediated immunity, potential autoimmune mechanism	
Interleukin-2	AKI	Capillary leak syndrome leading to prerenal AKI	Control volume and haemodynamic status Avoid other nephrotoxins
Rituximab	AKI, electrolyte disturbances	Tumour lysis syndrome	
Interferons	Proteinuria, nephrotic syndrome Thrombotic microangiopathy	Minimal changes	

AKI, acute kidney injury; SIADH, syndrome of inappropriate antidiuretic hormone secretion; DITMA, drug-induced thrombotic microangiopathy; VEGR, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; BRAF, v-Raf murine sarcoma viral oncogene homologue B; ALK, anaplastic lymphoma kinase; PD-1, programmed cell death protein 1; PDL-1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; GFR, glomerular filtration rate.

Renal effects of targeted therapies.



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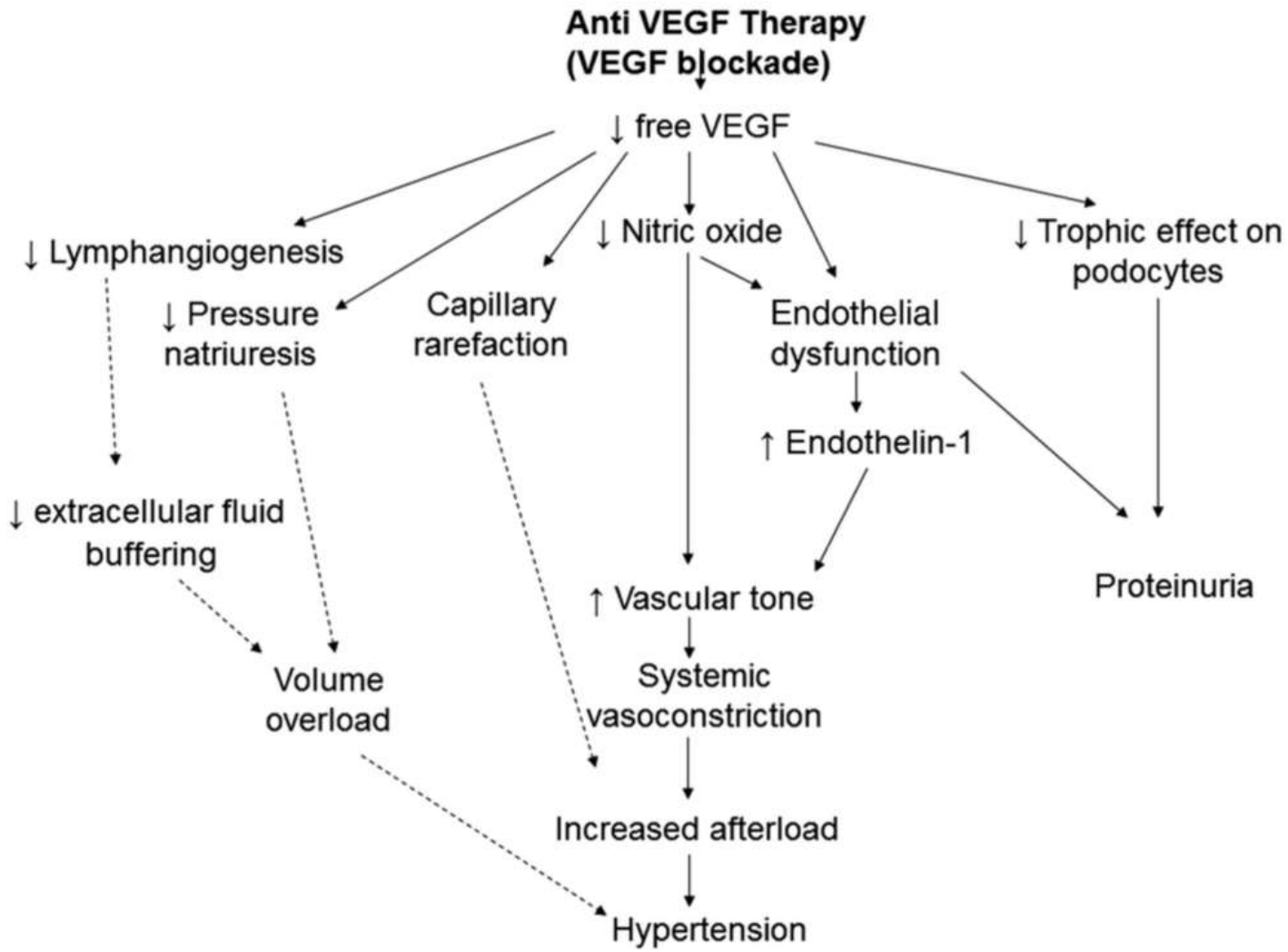

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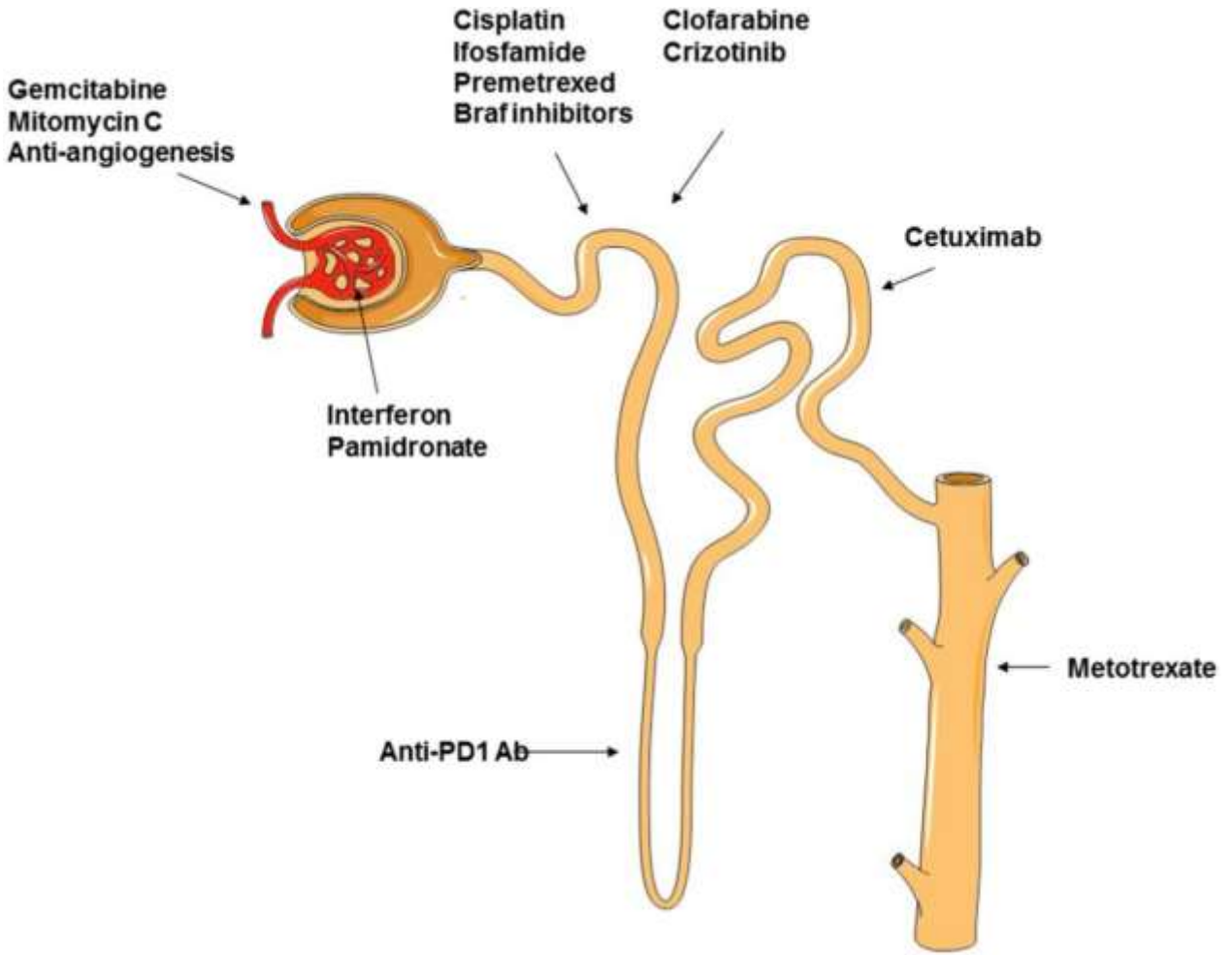
Chemotherapy-induced kidney injury.



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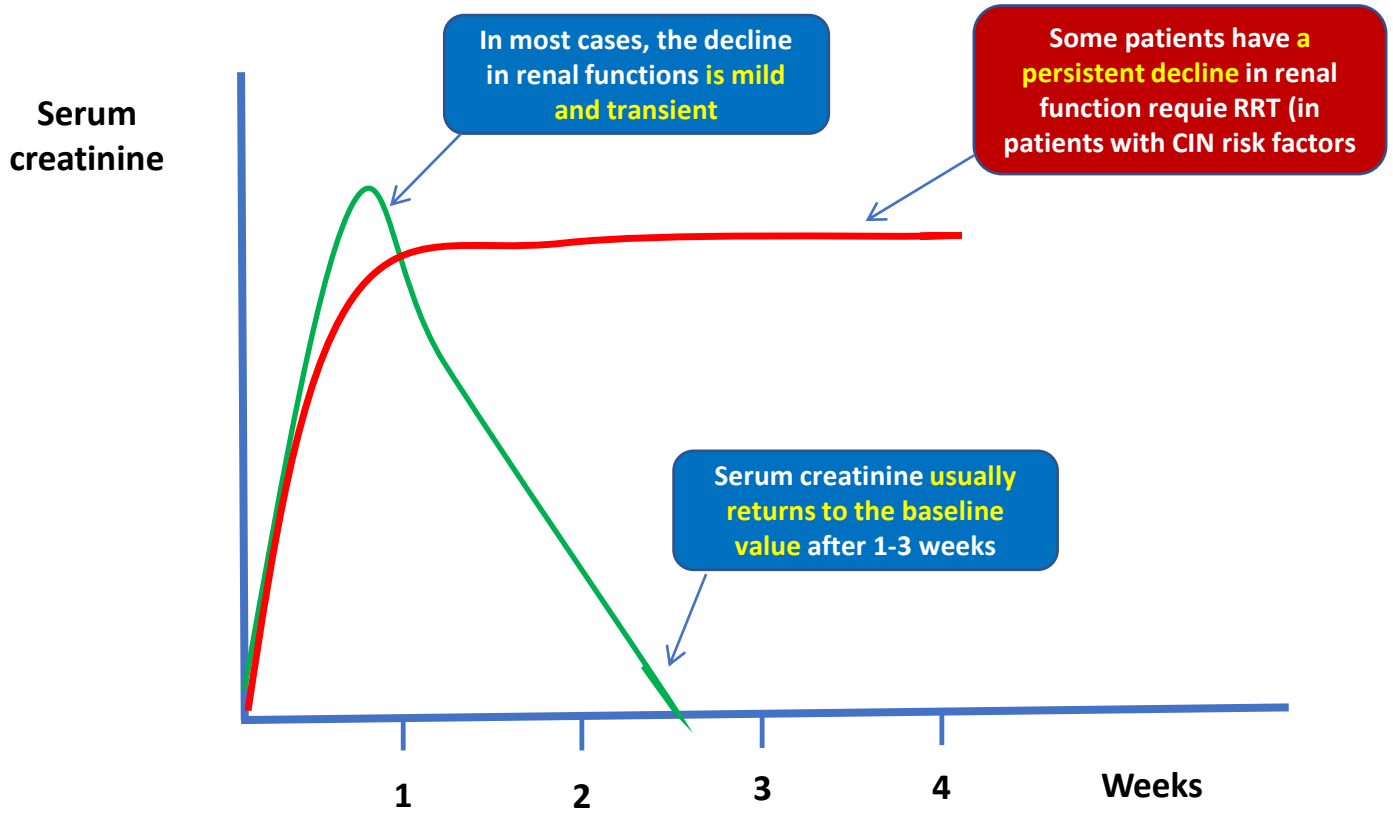
- A variety of renal disease and electrolyte disorders can result from the drugs that are used to treat malignant disease .
- The kidneys are a major elimination pathway for many antineoplastic drugs and their metabolites.
- There are two principal pathways for drug excretion by the kidney:
  - glomerular filtration and
  - tubular secretion.

- Chemotherapeutic agents can affect the glomerulus, tubules, interstitium or the renal microvasculature, with clinical manifestations that range from an asymptomatic elevation of serum creatinine to acute renal failure requiring dialysis

- So chemotherapy-induced kidney disease could be categorized as follows:
  - acute kidney injury (AKI) due tothrombotic microangiopathy (TMA),
  - toxic acute tubular necrosis,
  - crystal nephropathy,
  - proteinuria/nephrotic syndrome due to TMA,
  - focal segmental glomerulosclerosis (FSGS),
  - minimal change disease,
  - membranous nephropathy;
  - tubulopathies due to electrolyte, acid-base and
  - divalent disorders;
  - and chronic kidney disease (CKD) due to glomerulopathies or interstitial nephritis

Contrast-induced nephropathy

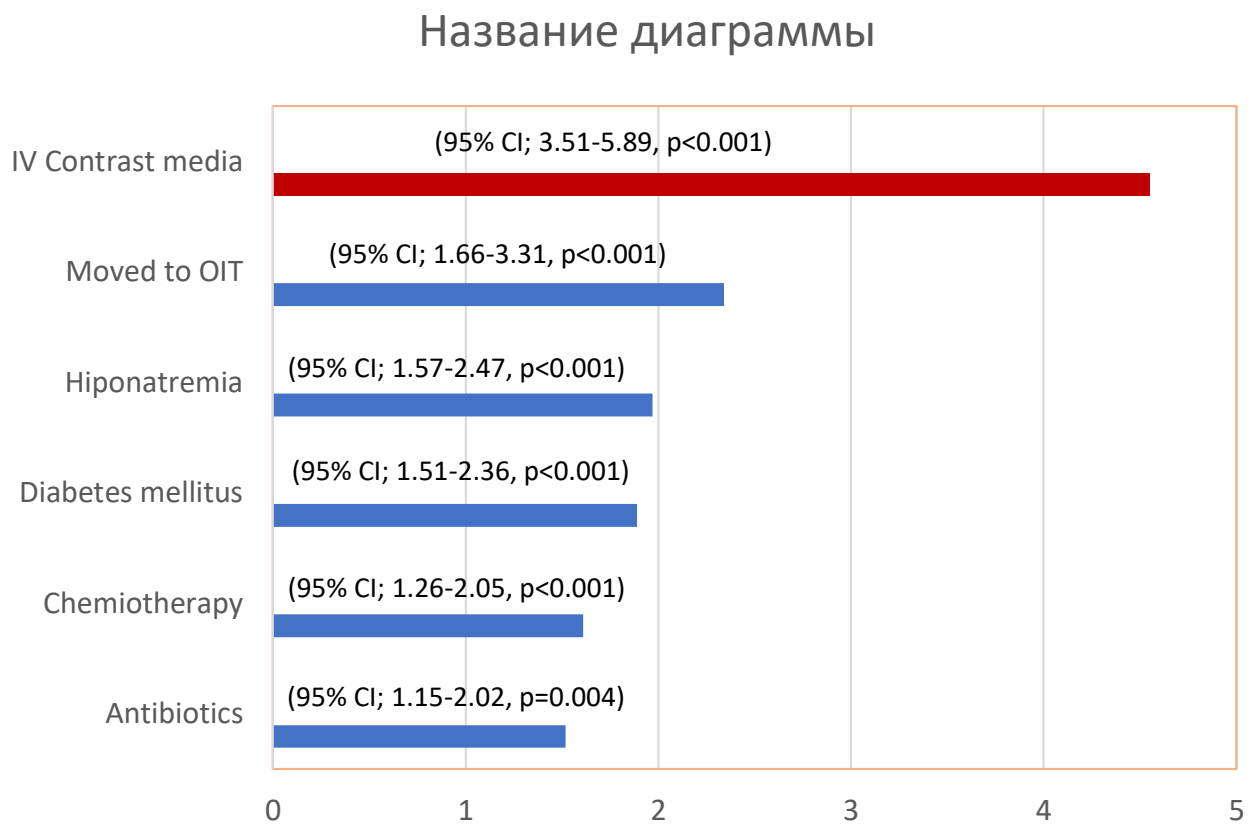
- Contrast-induced nephropathy (CIN) is an important drawback following administration of intravascular iodinated contrast agent
- Patients with cancer are treated with variety of nephrotoxic medications (chemotherapeutics, targeted drugs, antibiotics, analgesics and others).
- Additionally, other problems like anemia, hypercalcemia and hyperuricemia may also contribute to development of kidney damage in patients with malignancy.


Serum creatinine
In most cases, the decline in renal functions is mild and transient
Some patients have a persistent decline in renal function requie RRT (in patients with CIN risk factors
Serum creatinine usually returns to the baseline value after 1-3 weeks
1
2
3
4
Weeks

AKI

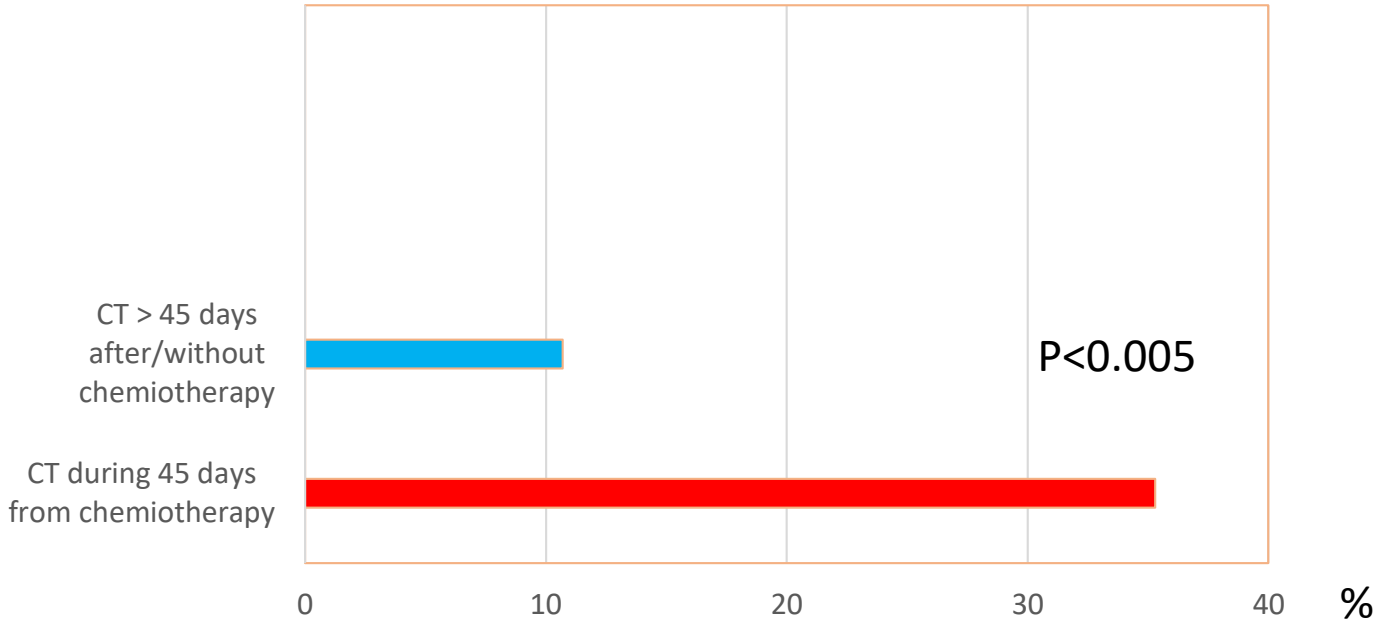
- Anderson Cancer Center, Texas, USA
- 3558 patients
- AKI – 12% patients (55% after 48 hours)
- Morbidity – 5 x (15.9 vs 2.7 %)
- Stay in hospital – 2x (10 vs 5 days)
- Cost – 106% (82835 vs 40164 $)

I.V Contrast media and AKI



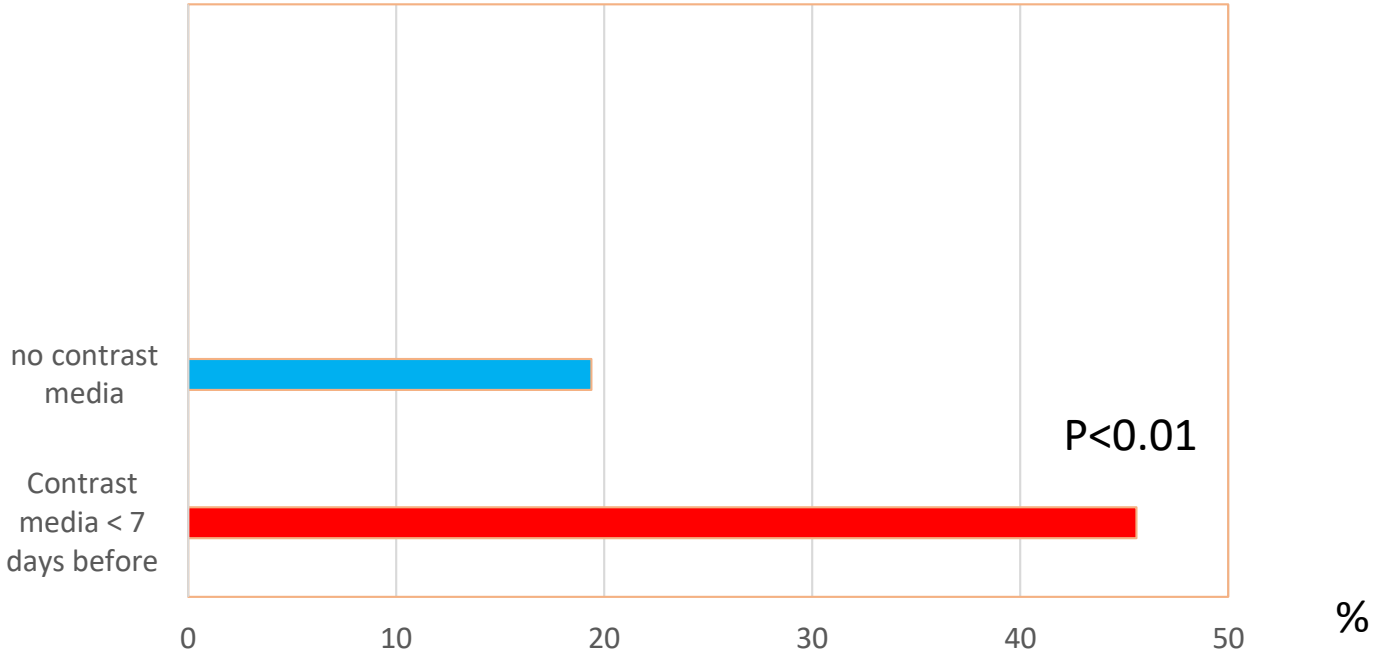
Chemotherapy before contrast media

- Prospective study
- 90 oncology patients, CT with contrast media
- GFR Before >50ml/min
- Before CT with contrast media fluid i.v. or p.o. 2000-3000 ml



Contrast media – risk for nephropathy

- 197 patients, chemotherapy agent – cisplatine
- Before treatment eGFR > 60ml/min
- All patients receive fluid i.v. 0.9% NaCl



In patients with nephropathy more CIN with contrast media

Chemotherapy and contrast media - nephropathy

	Chemotherapy	Contrast media
Endotelin, adenosine	+	+
Vasocontriction / hypoperfusion	+	+
Hypovolemia	+	+
Endothelial dysfunction	+	+
Inflammation/ free radicals O-	+	+
Direct toxicity	+	+

- Computed tomography with contrast (CT) appears to be standard and most common imaging procedure in oncology to monitor and evaluate the therapeutic response.
- Thus, the risk of CIN in patients with malignancy could be increased.
- Many cytotoxic and targeted medications as well as drugs for supportive care are contraindicated in the presence of impaired kidney function.
- Worsening of kidney function precludes or delays appropriate antineoplastic therapy.

Prevention


Indication for contrast – based procedures
Potential risk of CIN

What is optimal Hydration?

Estimating the Risk of Radiocontrast-Associated Nephropathy

Emilee Wilhelm-Leen, Maria E. Montez-Rath, and Glenn Chertow

Department of Medicine, Division of Nephrology, Stanford University School of Medicine, Palo Alto, California

J Am Soc Nephrol 28: 653–659, 2017. doi: 10.1681/ASN.2016010021

Table 3. Odds of AKI after contrast administration

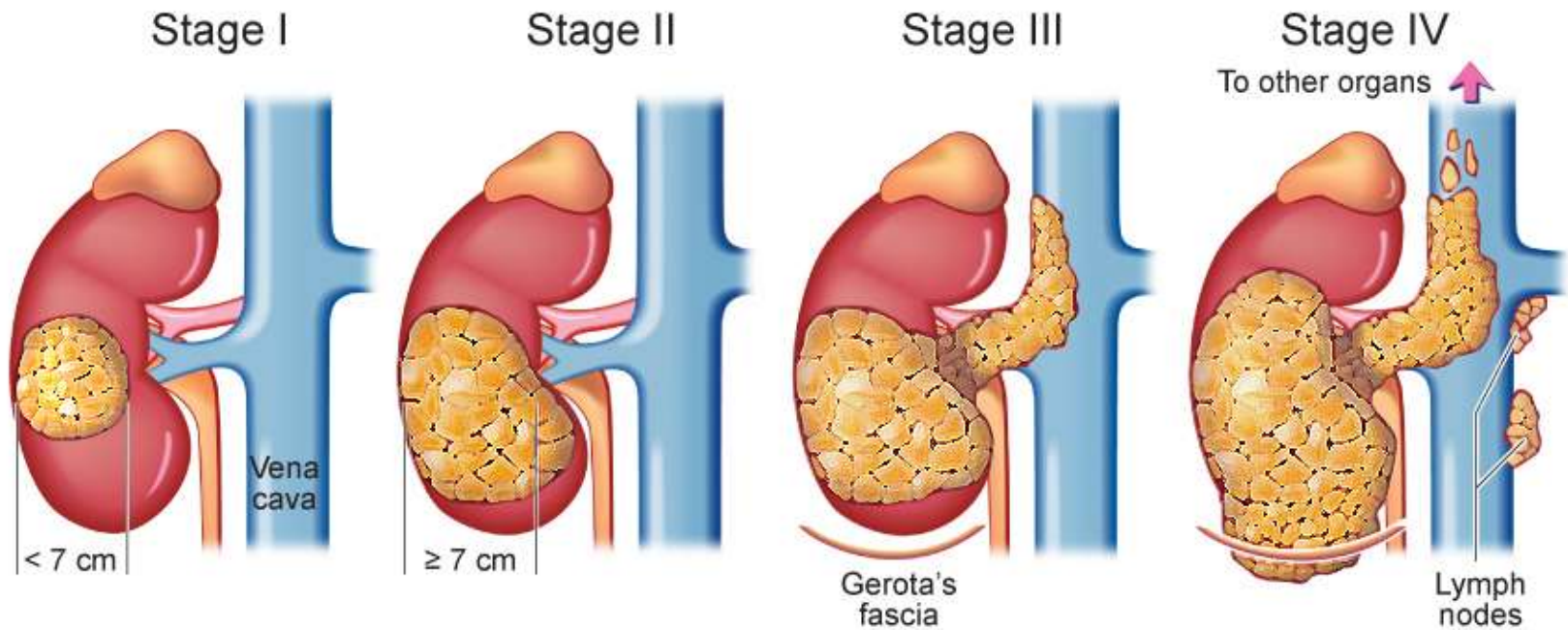
	Unadjusted Model		Adjusted[a] Model	
	Odds Ratio	**Adjusted Percentages**	**Odds Ratio**	**Adjusted Percentages**
No contrast	Reference	5.6 (5.4–5.8)	Reference	5.6 (5.4–5.8)
Contrast	0.98 (0.93–1.04)	5.5 (5.2–5.8)	0.93 (0.88–0.97)	5.1 (4.9–5.4)
c-statistic	0.50		0.81	

[a]Model adjusted for age, sex, mechanical ventilation, and combined comorbidity score. Parentheses contain 95% confidence intervals.

degree to which radiocontrast increases the risk of AKI. Although we await additional prospective data, we suspect that, on the basis of existing assumptions regarding attributable risk, diagnostic studies and some interventions that might save or improve lives are being withheld from patients owing to an exaggerated fear of radiocontrast nephropathy.

Patient with renal cancer

- Cancer in one kidney
- Cancer in two kidneys
- Cancer in second kidney (after nephrectomy)
  - Nephrectomy
  - Partial nephrectomy
  - chemiotherapy
  - Dialysis


Stage I
Stage II
Stage III
Stage IV
To other organs
Vena cava
< 7 cm
≥ 7 cm
Gerota's fascia
Lymph nodes

- Approximately 50% of all chemotherapeutics are excreted predominantly by the kidneys in urine as unchanged drug or active metabolite(s), thus, any impairment in kidney function may lead to accumulation of potentially toxic metabolites and overdosage.
- The dose of anticancer drugs in CKD patients should be adjusted to avoid severe toxicities .
- In addition, using chemotherapeutics with potential nephrotoxicity will also require specific monitoring and, when available, specific prevention reducing the risk for nephrotoxicity, especially in patients with preexisting CKD

- In stage 2 CKD subjects, potential nephrotoxicity of the therapy is the important and relevant issue.
- It has been shown that preexisting impairment in kidney function is a risk factor for nephrotoxicity caused by anticancer treatment .
- Thus, in patients with worsened kidney function, clinicians should take into account the potential risk of nephrotoxicity, and implement preventive measures whenever possible.
- However, in a case when administration of nephrotoxic agent is necessary, it is essential to adjust the dose, according to the kidney function and to follow the guidelines for the management of nephrotoxicity if available, as in a case of cisplatin

- Thus, it should be stressed that CKD is underrecognized problem in oncology population and eGFR is to be assessed simultaneously, not only in oncology ward but also in every department.
- This is due to the fact that patients are getting older, have more comorbidities, are administered more potentially nephrotoxic drugs and undergone more potentially nephrotoxic procedures such as percutaneous coronary interventions-PCI or CT with IV contrast agent etc.
- It is of utmost importance to be aware of the kidney function in patients receiving nephrotoxic or potentially nephrotoxic agent and to monitor kidney function regularly, before each course of chemotherapy.

- Oncologists should adjust the dose of cytotoxic drugs according to actual kidney function.
- Besides, in patients treated with nephrotoxic chemotherapeutic agents in particular with preexisting impairment of kidney function, the necessity of concomitant drugs should be carefully evaluated i.e.NSAIDS.
- They should be avoided, if possible, as they may contribute to the nephrotoxicity of chemotherapeutics.

Summary

- A plethora of renal problems may be found in patients with malignancy.
- They may influence not only their short-term outcomes but also the adequate therapy of the underlying oncological problem.
- Thus, all these kidney-related issues pose an important challenge for both specialities: oncology and nephrology.
- Indeed, the incidence rates for many malignancies are increased and amelioration in cancer mortality due to more effective chemotherapy, including targeted drugs, and treatment with stem cells, caused in a rise in population of cancer survivors

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Thank you