

How Would I Dose Chemotherapy?



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Multidisciplinary Dosing of Chemotherapy in Patients with Kidney Disease

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Disclosures

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- *President, Board of Directors: American Society of Onconeurology*



Learning Objectives

- 1) Understand the lack of robust evidence for renal dose adjustment of anticancer therapies
- 2) Review the approach to anticancer drug dosing in an exemplar case of carboplatin use in a patient with CKD
- 3) Review the principles of anticancer drug dosing in a patient receiving Kidney Replacement Therapy (KRT)



The Influence of Kidney Function on Cancer Therapy Decisions

- ‘Renalism’: Impacts therapy eligibility (both drugs/procedures) and dose-adjustment
- Drug Effects on eGFR
- Clinical trial enrollment

Table 1. Chemotherapeutic agents whose dosing is dependent on kidney function (GFR)

Timetable

Anthracyclines (except doxorubicin)
Bleomycin
Carboplatin
Cisplatin
Cladribine
Clofarabine
Dacarbazine
Eribulin
Etoposide
Fludarabine
Ifosfamide
Irinotecan
Mercaptopurine
Methotrexate
Oxaliplatin
Pemetrexed
Topotecan



Lack of Evidence-based Guidance

Exclusion of CKD from Trials of Cancer Therapy

- Systematic review of RCT for drugs for the 5 most common solid cancers (bladder, breast, colorectal, lung, and prostate) in 6 high-profile general medicine and oncology journals

Table 1. Characteristics of Randomized Clinical Trials of Anticancer Drugs Examined for the Exclusion of Patients With Chronic Kidney Disease

	Trials, No. (%)	Patients, No.	Trials Explicitly Excluding Kidney Disease, No. (%)	P Value^a
Overall	310 (100)	282 889	264 (85)	

Table 2. Thresholds Used for Exclusion of Patients With Kidney Disease in Randomized Clinical Trials of Anticancer Drugs (N = 264 Trials)^a

Measurement for Kidney Function–Based Exclusion ^a	No. of Trials (%) ^b	eGFR, mL/min/1.73 m ²	14 (5)
Serum creatinine value	162 (62)	<60	5 (2)
Serum creatinine value relative to ULN	129 (49)	<50	4 (2)
>ULN	16 (6)	<45	1 (0.4)
>1.25-times ULN	7 (3)	<30	4 (2)
>1.5-times ULN	93 (35)	Proteinuria	31 (12)
>2-times ULN	6 (2)	Nonspecified renal exclusion ^c	41 (16)
		Multiple exclusion criteria related to kidney function ^d	90 (34)



Are new cancer therapeutics being tested in patients with CKD?



Oncology drugs
approved 2015-2019



55 drugs



74 pivotal
trials

PIVOTAL TRIALS



kidney-related
eligibility criteria

95%

of trials



GFR-based
eligibility criteria

68%

of trials

creatinine
clearance

65%

GFR

8%

PHARMACOKINETIC ANALYSES

CKD
4 & 5

29%

of drugs

84%

creatinine
clearance

Dialysis



6%

of drugs

16%

GFR

NO KIDNEY DOSING INFORMATION



49%

of drugs

Conclusions: Patients with CKD are excluded from anticancer drug development. GFR estimation in pivotal trials and renal pharmacokinetic analyses remains imprecise and heterogeneous. Kidney-related safety and dosing information is scarcely and inconsistently presented.

Morgan A. Butrovich, Allison C. Reeves, Jamie Heyward, et al. ***Inclusion of Participants with CKD and Other Kidney-Related Considerations during Clinical Drug Development***. CJASN doi: 10.2215/CJN.000000000000105. **Visual Abstract by Joel Topf, MD, FACP**

Case 1

Carboplatin-dosing via Calvert Equation

- 77-year-old male, with invasive bladder cancer and heart failure, initiating carboplatin
- ECOG: 2
- Weight loss of 10 kg over 3 months
- Height: 1.75m, Weight: 95 kg (BMI 31 Kg/m², BSA 2.2 m²)
- Serum Cr: 1.17 mg/dL
- Serum Cys C: 1.65 mg/L
- 24-hour Urine CrCl: 102 mL/min

GFR calculation before treatment initiation

CG CrCl: 72.8 mL/min

CKD-EPI 2021 eGFR_{cr}: 78 mL/min

CKD-EPI 2021 eGFR_{cr-cys}: 60 mL/min

mGFR ⁵¹Cr-EDTA: 40 mL/min

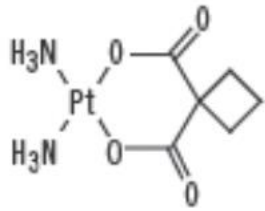
} Muscle mass
-dependent

← Lower mGFR



Dose Calculation via GFR

Carboplatin-dosing via Calvert Equation



Carboplatin Dosage: Prospective Evaluation of a Simple Formula Based on Renal Function

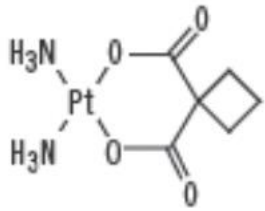
By A.H. Calvert, D.R. Newell, L.A. Gumbrell, S. O'Reilly, M. Burnell, F.E. Boxall, Z.H. Siddik, I.R. Judson, M.E. Gore, and E. Wiltshaw

A dosage formula has been derived from a retrospective analysis of carboplatin pharmacokinetics in 18 patients with pretreatment glomerular filtration rates (GFR) in the range of 33 to 136 mL/min.

$$\text{Carboplatin dose (mg)} = \text{target AUC ([mg/ml} \times \text{min)} \times \underline{(\text{GFR} + 25) \text{ (ml/min)}}$$

Dose Calculation via GFR

Carboplatin-dosing via Calvert Equation



CG-CrCl



Carboplatin dose (mg) = target AUC ([mg/ml]×min) × (GFR + 25) (ml/min)

1930s and
1940s-
Homer Smith
studies
glomerular
filtration rate



1976
Cockcroft-
Gault
equation for
estimated
creatinine
clearance



1989 Calvert
equation for
carboplatin
dosing



2009, 2012,
2021 CKD-
EPI equations
to estimate
glomerular
filtration rate
published



2012 KDIGO
advocates
abandoning
Cockcroft-Gault and
using estimated
glomerular filtration
rate



2022
Anticancer
Drug Dosing
in Kidney
Dysfunction
(ADDIKD)
guideline

Cr is both filtered +
secreted → CrCl may be
10%–40% higher than the
GFR as GFR declines

Implementation of IDMS
standardized Cr assay, SCr
values ↓ 10%–20%, thus
↑ Cockcroft-Gault estimated CrCl



Dose Calculation via GFR

Carboplatin-dosing via Calvert Equation

Formulae recently proposed to estimate renal glomerular filtration rate improve the prediction of carboplatin clearance

Melanie White-Koning^{1,2} · Marie Noëlle Paludetto^{1,2,3} · Félicien Le Louedec^{1,3} · Laurence Gladieff⁴ · Christine Chevreau⁴ · Etienne Chatelut^{1,2} · Florent PUISSET^{1,2,3} 

Formula	MAPE [95% CI]	P20 [95% CI]
vs Calvert-CKD-EPI-CysC	14.0 [12.9–15.2]	23 [19–26]
vs Calvert-CKD-EPI	15.3 [14.1–16.5]	28 [24–32]
vs Thomas	15.5 [14.3–16.8]	27 [23–31]
vs Calvert-Janowitz	15.8 [14.6–16.9]	32 [28–36]
vs Calvert-CG	16.3 [15.1–17.5]	34 [30–38]
vs Calvert-MDRD	17.2 [17.8–18.6]	34 [30–38]
vs Chatelut	21.2 [19.7–22.8]	46 [41–50]

“Calvert-CKD-EPI-CysC shows the best precision of all formulae and Calvert-CKD-EPI-Cr the best precision of creatinine-based formulae”



eGFR Discordance in Patients with Cancer

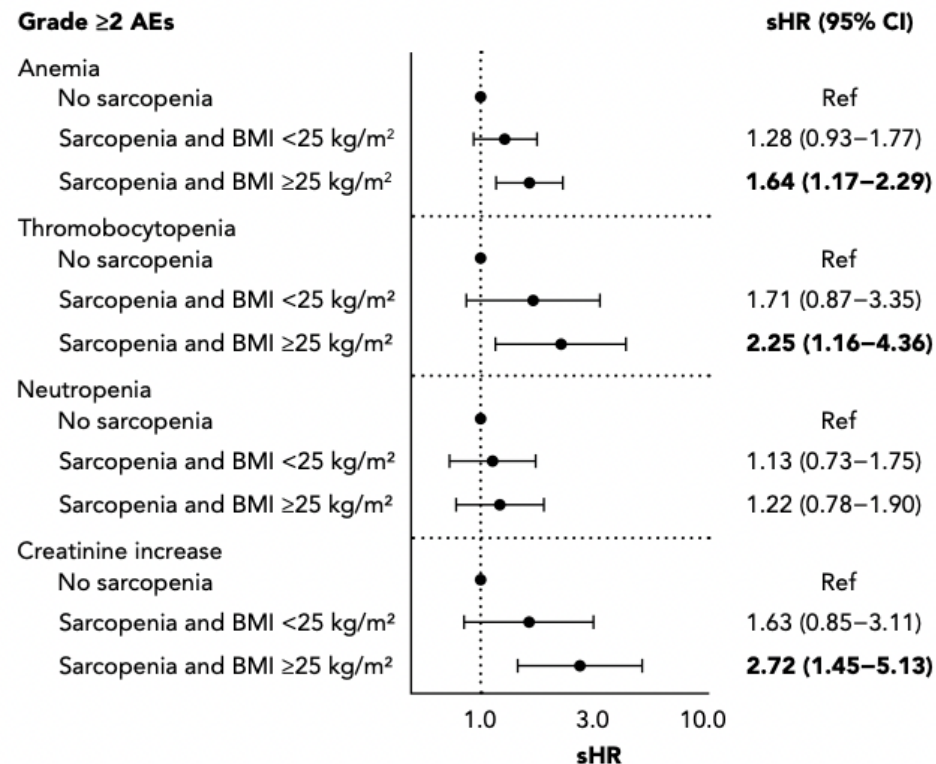
Sarcopenia and Adverse Events from Platinum Chemotherapy

Patients with NSCLC receiving cisplatin or carboplatin:

N = 604, CT-defined skeletal muscle and adiposity indices

Sarcopenia and elevated BMI (n= 67) was associated with increased risk of grade ≥ 2 adverse events

Patients whose Cockcroft-Gault–based glomerular filtration rate (GFR) dictated a carboplatin dose ≥ 25 mg higher than CKD-EPI GFR:



Adverse Events

Grade ≥ 2

Anemia
Thrombocytopenia
Neutropenia
Creatinine increase

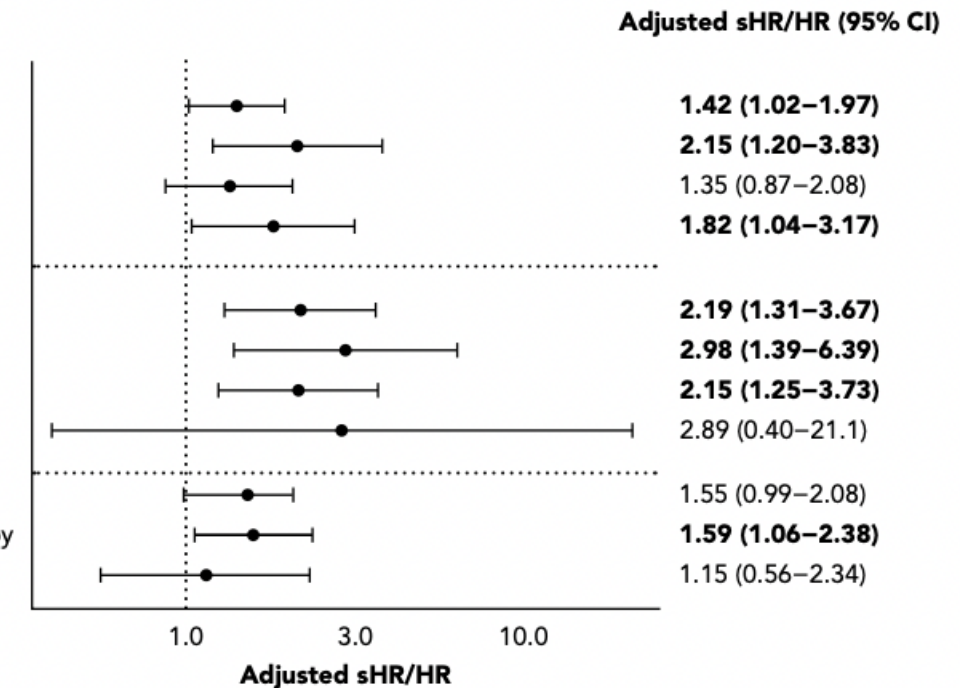
Grade ≥ 3

Anemia
Thrombocytopenia
Neutropenia
Creatinine increase

Hospitalization

Discontinuation of chemotherapy

Mortality



Body Surface-Area eGFR Adjustment

Carboplatin: Dosed via GFR only

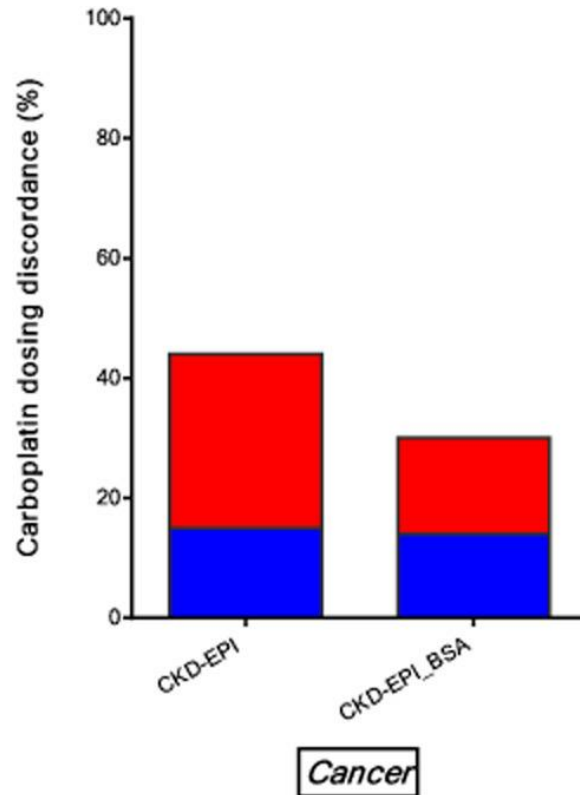


Table 5 Comparison of percentage of patients with MAPE over 20% and 95% confidence interval [95% CI] between predicting formulae (*p* values according to McNemar's test, *n* = 491)

Formulae	P20 [95% CI]	Adjusted <i>p</i> value						
		vs Calvert(CKD-EPI-CysC)	vs Calvert CKD-EPI	vs Thomas	vs Calvert-Janowitz	vs Calvert CG	vs Calvert-MDRD	vs Chatelut
vs Calvert-CKD-EPI-CysC	23 [19–26]	1	0.009 ^a	0.007 ^a	<0.001 ^a	<0.001 ^a	<0.001 ^a	<0.001 ^a
vs Calvert-CKD-EPI	28 [24–32]		1	0.780	0.026 ^a	0.004 ^a	0.005 ^a	<0.001 ^a
vs Thomas	27 [23–31]			1	0.085	0.013 ^a	0.034 ^a	<0.001 ^a
vs Calvert-Janowitz	32 [28–36]				1	0.397	0.714	<0.001 ^a
vs Calvert-CG	34 [30–38]					1	0.663	<0.001 ^a
vs Calvert-MDRD	34 [30–38]						1	<0.001 ^a
vs Chatelut	46 [41–50]							1

^aStatistically significant at the 5% level

- 1) BSA correction for carboplatin allows for less discordant dosing vs mGFR
- 2) CKD-EPI with BSA correction best predicts measured carboplatin clearance

Case 1

Carboplatin-dosing via Calvert Equation

GFR calculation before treatment initiation

CG CrCl: 72.8 mL/min

CKD-EPI 2021 eGFR_{cr}: 78 mL/min

CKD-EPI 2021 eGFR_{cr-cys}: 60 mL/min

mGFR ⁵¹Cr-EDTA: 40 mL/min

Cumulative dose after the fourth cycle of chemotherapy

Cumulative Carboplatin Dose per Calvert Equation using
CG CrCl: 1,960 mg (received)

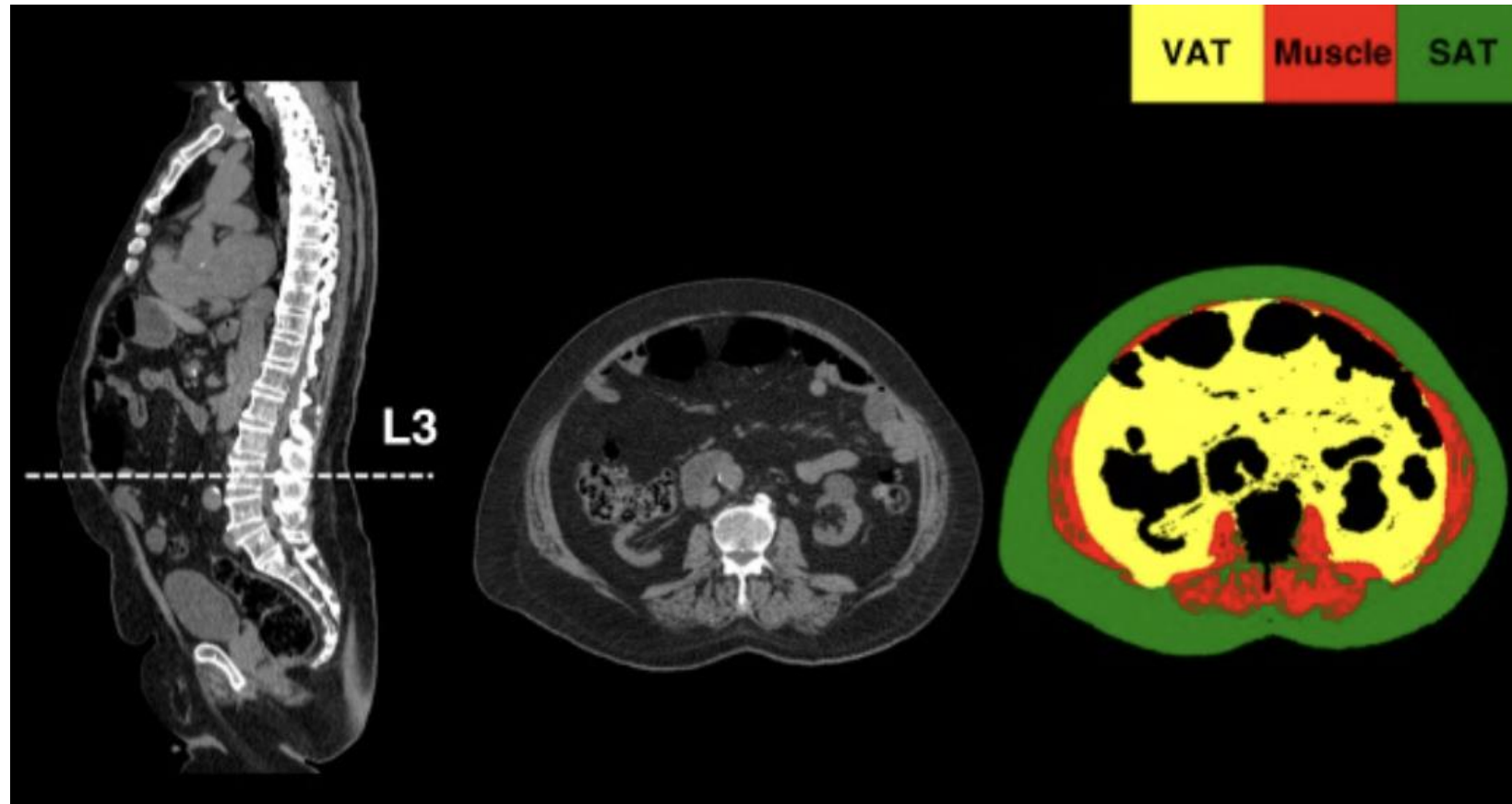
Cumulative Carboplatin Dose per Calvert Equation using
mGFR: 1,300 mg (ideal)

↑46%
In dose



Case 1

Carboplatin-dosing via Calvert Equation



Body composition parameters calculated from his CT scan demonstrated sarcopenia. His skeletal muscle index was 50.5 cm^2/m^2



Case 1

Carboplatin-dosing via Calvert Equation

After 4 cycles of chemotherapy, he was admitted to the hospital with sepsis due to pneumonia. His laboratory studies showed neutropenia, thrombocytopenia, and acute kidney injury (Cr: 5.1 mg/dL) requiring dialysis. He died two weeks later due to sepsis-associated multiorgan dysfunction



eGFR-based Carboplatin Dose Modification

Key Messages from ASON Position Statement

3.1: Cautious use of body surface-area (BSA) adjustment (e.g., correction for patients' actual BSA) when estimating GFR for the purpose of carboplatin dose-adjustment in patients with cancer is appropriate. For other anticancer drugs, standardized (i.e., BSA-indexed) GFR estimates are appropriate for drug dose-adjustment.

3.2: Use of a measured GFR (mGFR) via an exogenous filtration marker in patients with cancer and atypical body habitus (e.g., obesity, sarcopenia/underweight, extremes of height, etc.) to guide cancer drug eligibility and dose-adjustment should be considered



Case 1

Consensus Guidance for Carboplatin-dosing via Calvert Equation

International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)

2022



Carboplatin Dose Calculator

Kidney Function: ☒ BSA Adjusted eGFR_{CKD-EPI} ☐ Directly Measured GFR (mGFR) ☐ Creatinine Clearance (CrCl)

Date of Birth:

select day of month

select month

select year

OR

Age:*

Age

Sex:*

☐ Male ☐ Female

Height:*

centimetre

Height

Actual Body Weight:*

kilogram

Weight

BSA Formula:

☒ Dubois and Dubois ☐ Mosteller

Serum Creatinine*

micromol per litre

Serum Creatinine

**Target Area Under the
Curve (AUC):***

5



Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) Guideline

Sandhu G *et al.* *International consensus guideline on anticancer drug dosing in kidney dysfunction.* 2022. eviQ, Cancer Institute NSW.

ANTICANCER DRUG DOSE RECOMMENDATIONS		
eGFR (mL/min/1.73 m ²)	Dose	Comment
≥ 60	full dose	
45 – 59	full dose	Increased risk of adverse events.
30 – 44	reduce by 25% ^{a,b} or alternative protocol	Consider a 25% dose reduction in patients with <i>either</i> : • non-curative treatment intent • concomitant nephrotoxic drug exposure • a poor performance status. In all other patients, consider a clinically appropriate alternative treatment protocol
15 – 29	AVOID	Increased risk of adverse events.
< 15 (without KRT)		
KRT	Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.	

Green – “go” – proceed with full dose

Yellow – “wait” - dose adjustment, closer monitoring for drug-related adverse events and/or special cautions to consider

Red – “stop” - do not proceed.

^a Dose adjustment may require rounding to nearest capsule strength to enable delivery of a measurable dose.

^b The dose reduction applies to each individual dose and not to the total number of days or duration within the treatment cycle.

Abbreviations: eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease – Epidemiology Collaboration equation; KRT, kidney replacement therapy.

Footnotes with drug specific practice points

Case 2

Chemotherapy Dose Adjustment in Patients Receiving KRT

- 41-year-old male
- **Metastatic seminoma**, lymph node involvement
- **RFR**: “Dose adjustment of chemotherapy in ESKD”
- **Past Medical History** : Endstage Kidney Disease receiving intermittent hemodialysis thrice weekly, Monday/Wednesday/Friday
- **Starting chemotherapy – proposed regimen**:
 - Bleomycin
 - Etoposide
 - Cisplatin



Approach to Dose Adjustment of Systemic Therapy

Considerations in Advanced CKD/ESKD & KRT

Cancer Prognosis and
Intent of Systemic
Therapy:

Curative vs. Palliative
Treatment?

Patient Age,
Comorbidities, and
Current Clinical Status:

Vitals signs, Laboratory
Parameters

Pharmacokinetics and
Pharmacodynamics of
Systemic Therapy Drugs

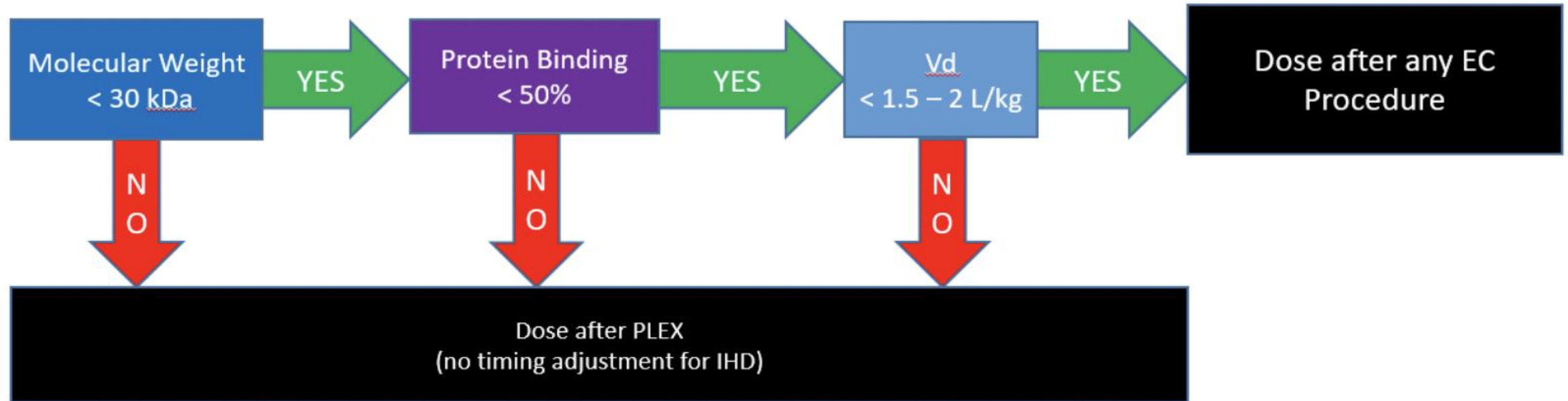
Literature Review and
Case Reports/Series

Characteristics of
Kidney Replacement
Therapy Modality
and Residual Kidney
Function



Dose Adjustment of Systemic Therapy

Drug Removal with Extracorporeal (EC) Treatment



Case 2

Regimen Modification in Dialysis

Agent	Metabolism	Elimination	MW (Da)	Protein Binding (%)	Vd (L/kg)	Dialyzability
Bleomycin	Hydrolases in multiple tissues (most in hepatic/GI)	Urine (66% unchanged)	1500	<1	0.3	Minimal
Etoposide	Hepatic	Urine (29% unchanged)	588.6	74-94	0.17-0.5	Minimal
Cisplatin	Non-enzymatic aquation in multiple tissues and plasma	Urine (27-45% unchanged)	300	>90	0.5	Unbound/free Component



Case 2

Regimen Modification in Dialysis

Agent	Metabolism	Elimination	MW (Da)	Protein Binding (%)	Vd (L/kg)	Dialyzability	Literature Review/ Comments
Bleomycin	Hydrolases in multiple tissues (most in hepatic/GI)	Urine (66% unchanged)	1500	<1	0.3	Minimal	60% dose reduction or omission – high risk of pulmonary toxicity No timing considerations around HD
Etoposide	Hepatic	Urine (29% unchanged)	588.6	74-94	0.17-0.5	Minimal	50% dose reduction No timing considerations around HD
Cisplatin	Non-enzymatic aquation in multiple tissues and plasma	Urine (27-45% unchanged)	300	>90	0.5	Unbound/free Component	50% dose reduction After HD or non-dialysis day vs high dose regimens: 1 – 2 h pre-HD

Case 2

Regimen Modification in Dialysis

Agent	Literature Review/ Comments	Standard Dosing (21 day cycle x 3)	Case 4 Example Dosing (21 day cycle x 4)
Bleomycin	60% dose reduction or omission – high risk of pulmonary toxicity No timing considerations around HD	Bleomycin 30 units IV weekly	Bleomycin omitted Alternative: Consideration of Bleomycin 12 units IV weekly
Etoposide	50% dose reduction No timing considerations around HD	Etoposide 100 mg/m² days 1-5	Etoposide 50 mg/m² Days 1-5
Cisplatin	50% dose reduction After HD or non-dialysis day vs high dose regimens: 1 – 2 h pre-HD	Cisplatin 20 mg/m² days 1-5	Cisplatin 10 mg/m² days 1, 3, 5 (post-HD) Alternative: Consideration of Cisplatin 40 mg/m ² pre-HD

Future Directions

Dose Adjustment of Cancer Therapies in CKD

- Advocacy for regulatory body (e.g., FDA, EMA, Health Canada) requirements for PK, PD (and pharmacogenetics) data in the eGFR ranges where drugs may be frequently prescribed
- Multidisciplinary input for clinical trial design (oncology, nephrology, pharmacy):
 - i. Inclusion of kidney safety endpoints in trials of anticancer therapies
 - ii. Appropriate patient inclusion/exclusion criteria based on appropriate kidney health assessment
 - iii. Subgroup analyses of patients with CKD and KRT in clinical trials of anticancer therapy (or parallel trials for this population)
 - iv. Post-marketing safety studies of patients with advanced CKD and KRT
- **Multidisciplinary consensus dosing guidelines informed by the above data**

Summary Points (1)

Dose Adjustment of Cancer Therapies in CKD

- Numerous drugs warrant dose modification according to kidney function, requiring individualization and balancing toxicity vs efficacy considerations
 - Major limitations remain: exclusion from clinical trials, and lack of PK/PD data
- Dosing therapies with GFR-based eligibility or dose modification requires optimal GFR assessment and interpretation with consideration of body composition
 - GFR assessment via validated contemporary estimating equations (where possible) incorporating creatinine and cystatin C (e.g., $\text{CKD-EPI}_{\text{Cr-CysC}}$). Consideration of mGFR when accuracy will effect eligibility/dosing.
 - Carboplatin dosing via Calvert equation should use BSA-adjusted eGFR
 - Use of international consensus approaches (e.g. ADDIKD guidelines) is recommended

Summary Points (2)

Dose Adjustment of Cancer Therapies in CKD

- Dosing of anticancer therapies in KRT requires a multidisciplinary approach incorporating:
 - Review of pharmacokinetics/pharmacodynamics
 - Drug dialyzability (molecular weight, protein binding and volume of distribution)
 - Available reported cases/series
- Avoid precluding patients with CKD from potentially beneficial therapy!

Thank You

Questions/Discussion

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