Integrating International Consensus Guidelines for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) into everyday practice

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Summary

Part 2 of the International Consensus Guideline on Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) offers drug-specific consensus recommendations based on both evidence and practical experience. These recommendations build upon the kidney function assessment and classification guidelines established in Part 1 of ADDIKD. Here we illustrate how dosing recommendations differ between ADDIKD and existing guidance for four commonly used drugs: methotrexate, cisplatin, carboplatin and nivolumab. We then describe how the recommendations can be distilled into practice points for methotrexate and cisplatin. While ADDIKD is a significant improvement from previous guidelines, adoption of this new guideline requires further endorsement from key external stakeholders, 'change championing' by clinicians locally and encouraging its integration into existing reference sources, clinical trial protocols and electronic prescribing systems.

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Keywords: Chemotherapy; Drug dosing; Kidney dysfunction; Renal; Oncology; Haematology; Pharmacokinetics

Research in context

Evidence before the study
High quality evidence for anticancer drug dosing in reduced kidney function is limited and no internationally agreed guidelines exist to inform prescribing decisions in this population.

Added value of this study
The International Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) standardised the assessment of kidney function (Part 1) and its application to anticancer drug dosing using published evidence and expert consensus (Part 2). Here, we have selected four widely prescribed anticancer drugs (methotrexate, cisplatin, carboplatin and nivolumab) to illustrate how ADDIKD's drug specific recommendations compare to previously published guidance. The challenges of implementing ADDIKD into clinical practice are also discussed.

Implications of all the available evidence
An internationally standardised, evidenced- and consensus-based approach to the dosing cancer patients with abnormal kidney function was much needed resource clinically, and adoption into regulatory drug processes within government and the pharmaceutical industry envisaged. Ongoing review of emerging evidence, inclusion of new anticancer drugs and incorporation of patients on kidney replacement therapy into ADDIKD will need to be considered for future updates.

Introduction

The International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)[1] was developed in two parts, with Part 1 providing three recommendations for the assessment and classification of kidney function in cancer patients [unpublished].[2] In Part 2, consensus recommendations for 59 anticancer drugs were formulated on both evidence and practice-based decisions [unpublished][3] (see Supplementary Material 1 for a summary of ADDIKD's drug specific recommendations).

ADDIKD has been widely endorsed internationally, including by the International Society of Geriatric Oncology, British Oncology Pharmacy Association, Haematology Society of Australia and New Zealand, Medical Oncology Group of Australia, Clinical Oncology Society of Australia, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Advanced Pharmacy Australia [AdPha] (formerly Society of Hospital Pharmacists of Australia), Australian and New Zealand Urogenital and Prostate Cancer Trials Group and The UK Renal Pharmacy Group. Kidney Disease: Improving Global Outcomes (KDIGO), AdPha and the American Society of Onco-Nephrology have included ADDIKD's recommendations in their position statements and guidance.

In this paper, we have selected four widely prescribed anticancer drugs (methotrexate, cisplatin, carboplatin and nivolumab) to illustrate how ADDIKD's drug specific recommendations compare to previously published guidance such as the Renal Drug Database,[4] regulatory-approved product information,[5] dose adjustment recommendations by BC Cancer's drug monographs,[6] articles by Krens and colleagues,[7,8] and Australia's eviQ treatment protocols (pre-ADDIKD implementation into its protocols [before July 2023]).[9] For methotrexate and cisplatin, we demonstrate how ADDIKD can be practically incorporated into a dosing guide for cancer clinicians.

Exemplar anticancer drugs

Methotrexate

Methotrexate is an anticancer drug administered via several routes (orally and parenterally) and used in the management of multiple malignancies including those requiring high plasma concentrations to achieve adequate tumour cell kill.[10,11] Methotrexate has a wide dosing range and is associated with high variability in interpatient pharmacokinetics.[12] The adverse event profile depends on the dosing (and consequential drug exposure), and high doses (≥ 500 mg/m^2) can cause serious adverse events including acute kidney injury (AKI).[13,14]

Existing guidelines propose methotrexate dose adjustments in reduced kidney function (Table 1); however, there are notable inconsistencies such as the kidney function threshold for discontinuation (varies between creatinine clearance [CrCl] or glomerular filtration rate [GFR] of 10–30 mL/min). Furthermore, there is little information on how tumour type, intent of treatment or dosing levels should influence dose recommendations.

As shown in Table 1, ADDIKD's guidance distinguishes high-from low-dose methotrexate and curative from non-curative treatment intent (see Supplementary Material 2 for ADDIKD's complete methotrexate dosing recommendations).[1] Unlike other guidance, when prescribing high-dose methotrexate, ADDIKD strongly recommends the utilisation of directly measured glomerular filtration rate (through direct measurement of the clearance of exogenous markers such as iohexol, iothalamate, ^{51}Cr-EDTA or ^{99m}Tc-DTPA and expressed in mL/min)[15,16] at baseline rather than an estimated assessment (i.e., estimated glomerular filtration rate [eGFR], CrCl). By way of a specific example, overall survival of patients with primary central nervous system lymphoma (PCNSL) relies on high-dose methotrexate to penetrate the blood–brain-barrier.[17,18] Existing guidelines empirically halve the dose of methotrexate when CrCl or GFR is 20–50 mL/min, whereas ADDIKD enables tailoring of the extent of dose reduction, by considering treatment intent and/or additional patient factors into more discrete bands according to the KDIGO Chronic Kidney Disease (CKD) categories of kidney function. Being curative, high-dose methotrexate in PCNSL patients (with a good performance status) who have an eGFR between 45–59 mL/min/1.73 m^2 (or

<table>
<tr><th>eGFR (mL/min/1·73 m^2)</th><th>ADDIKD[1]</th><th>eviQ[9]</th><th>BC Cancer[6]</th><th>Krens, et al.,[7] Giraud, et al.,[8]</th><th>Renal Drug Database[4]</th><th>Product Information[5]</th></tr>
<tr><td>≥ 60</td><td>Full dose</td><td>Full dose</td><td>CrCl > 80 mL/min: Full dose
CrCl 60 – 80 mL/min: reduce by 25%</td><td>Full dose</td><td>Full dose</td><td>Full dose</td></tr>
<tr><td>45 – 59</td><td>Dose < 500 mg/m^2: alternative protocol[a] or reduce by 25%
Dose ≥ 500 mg/m^2: full dose[a] or reduce by 25% or alternative protocol</td><td rowspan="2">CrCl 50 – 59 mL/min: full dose
CrCl 30 – 50 mL/min: reduce by 50%[b]</td><td>CrCl 51 – 60 mL/min: reduce by 30%</td><td rowspan="2">GFR 50 – 59 mL/min: full dose
GFR 20 – 50 mL/min: reduce by 50%</td><td rowspan="2">GFR 50 – 59 mL/min: full dose
GFR 20 – 50 mL/min: reduce by 50%
Correction for kidney function may be made by reducing the dose in proportion to the reduction in CrCl based on a CrCl 60 mL/min</td><td rowspan="2">Caution in significant reduced kidney function. Drug dosage should be reduced or discontinued until kidney function is improved or restored</td></tr>
<tr><td>30 – 44</td><td>alternative protocol or reduce by 50%</td><td rowspan="2">CrCl 10 – 50 mL/min: reduce by 50-70%</td></tr>
<tr><td>15 – 29</td><td rowspan="2">Avoid</td><td rowspan="2">Avoid</td><td rowspan="2">GFR < 20 mL/min: Avoid</td><td>GFR 10 – 20 mL/min: reduce by 50%
GFR < 10 mL/min: Avoid</td><td rowspan="2">Avoid</td></tr>
<tr><td>< 15 (without KRT)</td><td>CrCl < 10 mL/min: Avoid</td></tr>
</table>

Abbreviations: CrCl, creatinine clearance calculated using the Cockcroft–Gault equation; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease—Epidemiology Collaboration equation; GFR, glomerular filtration rate (not standarised to body surface area); KRT, kidney replacement therapy. a In patients with curative intent, good performance status and no concomitant nephrotoxic drugs. b Certain protocols with higher doses of methotrexate had more conservative dose adjustments.

Table 1: **Comparison of ADDIKD's recommendations vs existing guidance for methotrexate dosing according to kidney function.**

directly measured GFR between 45–59 mL/min) should maintain full doses, thereby ensuring dose exposure without significantly increasing toxicity.[19,20] ADDIKD recommends a 25% dose reduction or using an alternative protocol in patients not receiving curative treatment and/or poorer performance status. For example, if considering the use of low-dose methotrexate protocols, such as for breast cancer, alternative regimens without methotrexate demonstrate similar survival outcomes and do not increase the risk haematological and kidney-related adverse events.[21–23]

In addition to the specific dosing adjustments shown in Table 1, ADDIKD includes a set of 'practice points' to guide the administration of methotrexate (see Fig. 1).

Cisplatin

Cisplatin can be nephrotoxic,[24,25] with 20–50% excreted by the kidneys.[26–28] In addition, it has broad dosing ranges and is used in the treatment of many different tumours. Despite the widespread use of cisplatin, there is a paucity of evidence supporting dose adjustment recommendations in patients with reduced kidney function. Several studies have reported significantly poorer overall survival in patients with eGFR < 60 mL/min/1.73 m^2 who received reduced doses compared to patients with normal kidney function receiving full doses (at ≥ 50 mg/m^2 [inclusive of total fractionated doses]).[29–31]

In the absence of robust evidence, existing guidelines suggest generalised dose adjustments for a range

Practice points

- In **all patients**, to minimise the risk of methotrexate-induced AKI (acute kidney injury), preventative measures are advised:
  - Avoid concomitant administration of drugs that inhibit kidney tubular secretion and/or have additive nephrotoxic potential (especially for 24 hours before or after methotrexate administration) [refer to Appendix 5 of the ADDIKD guideline for a list of nephrotoxic anticancer drugs].[1,24-26]
  - Drain third-space effusions prior to treatment to prevent methotrexate distribution to these compartments and the consequences of delayed elimination.[24-26]
  - Monitor kidney function before, during and after methotrexate administration to ensure early identification of deterioration in kidney function.[24]
- In patients receiving **high-dose methotrexate (≥ 500 mg/m^2)**, additional supportive care measures are required to minimise the risk of methotrexate-induced AKI:
  - Maintain intravenous hydration, adequate urinary output, fluid balance and urinary alkalinisation (urine pH > 7) before, during and after methotrexate administration as per treatment protocol.[24-27]
  - Administer pharmacokinetically-guided calcium folinate (leucovorin) rescue, starting 24 – 36 hours post completion of methotrexate infusion (as per treatment protocol) until plasma methotrexate concentrations are at least < 0·1 µmol/L by 72 hours.[24-26]
  - Monitor methotrexate plasma concentrations every 24 hours from the completion of the methotrexate infusion, with prompt intervention (including consultation with clinical pharmacology, medical toxicology and/or clinical pharmacy) if plasma concentrations are elevated at 48 hours (as per nomogram) to avoid life-threatening toxicity.[25,26] Interventions may include intensification of calcium folinate (leucovorin), glucarpidase and/or dialysis (in rare circumstances), but are dependent on the time since methotrexate infusion, kidney function and timely access to the intervention.[25,26,28-30]
- The bioavailability of oral methotrexate is highly variable and dose dependent.[31] The dose recommendations listed do not account for additional dose adjustments required when converting between intravenous and oral methotrexate.
- Oral dose adjustments may require rounding to nearest tablet strength to enable delivery of a measurable dose.
- The dose reduction applies to each individual dose within the treatment cycle. For a continuous infusion, the dose reduction refers to the total dose and not the total duration of the infusion per treatment cycle.

Fig. 1: Methotrexate dosing practice points from ADDIKD.[1]

of tumour types without tailoring to treatment intent or dosing ranges (Table 2). Existing guidelines do not wholly consider factors which increase kidney-related adverse events such as concomitant nephrotoxic drug usage,[32,33] and performance status of the patient.[32] Large variations in dose adjustments for reduced kidney function are evident, with some guidelines recommending 25–50% dose reduction for CrCl or GFR 30–59 mL/min whilst others suggest when CrCl or GFR is < 40 mL/min, cisplatin is contraindicated.

ADDIKD's guideline for cisplatin incorporates several new factors for dose consideration. Firstly, dividing cisplatin dosing into high versus low-dose with a cut-off dosing level of 50 mg/m^2 [inclusive of total fractionated doses] (Table 2).[1] This dosing determination was based on the potential risk of high peaks of free platinum concentrations leading to cisplatin-induced adverse kidney events. High peaks are associated with doses > 50 mg/m^2, more frequent administration, a larger cumulative dose, and hypoalbuminaemia.[34–37] Secondly, dose adjustment recommendations were aligned with KDIGO CKD categories of kidney function and therefore tailor dose adjustments to more discrete bands compared to existing guidance.

Particularly in the eGFR 45–59 mL/min/1.73 m^2 category, ADDIKD recommends a dose reduction of high-dose cisplatin or considering an appropriate alternative treatment protocol with specific consideration of performance status and/or concomitant nephrotoxic drug exposure (see Supplementary Material 3 for ADDIKD's complete cisplatin dosing recommendations) [refer to Appendix 5 of the ADDIKD guideline for a list of nephrotoxic anticancer drugs].[1] In the supporting text of the guideline, ADDIKD gives the option of splitting full dose cisplatin into divided doses a week apart, thereby enabling patients with a good performance status with certain cancers (such as advanced urothelial cancer) to receive gold-standard treatment.[38,39] This is preferable to omitting or dose reducing cisplatin as per current guidelines.

ADDIKD also tailors its guidance for patients treated with curative intent. Patients with a good performance status receiving ≤ 50 mg/m^2 of cisplatin in the absence of concomitant nephrotoxic drugs are recommended full dose at eGFR 45–59 mL/min/1.73 m^2. Lelli et al., showed the rates of vomiting, haematological toxicities, and kidney-related adverse events in patients with reduced kidney function (eGFR 40–59 mL/min/1.73 m^2) receiving dose adjusted cisplatin (40–70% dose reduced) were comparable to those with normal kidney function receiving full dose cisplatin (50 mg/m^2).[40] In line with current guidelines, ADDIKD recommended avoiding cisplatin when eGFR < 45 mL/min/1.73 m^2, given there is no significant evidence to support its safe use in reduced kidney function, especially when alternative, less nephrotoxic treatment regimens may be appropriate.

Finally, in contrast to existing guidelines, ADDIKD recommends preventative and supportive care

eGFR (mL/min/1·73 m^2)	ADDIKD[1]	eviQ[9]	BC Cancer[6]	Krens, *et al.*,[7] Giraud, *et al.*,[8]	Renal Drug Database[4]	Product Information[5]
≥ 60	Full dose	CrCl ≥ 70 mL/min: full dose	Full dose	Full dose	Full dose	Full dose
45 – 59	Dose ≤ 50 mg/m^2: full dose[a] or reduce by 25% or alternative protocol Dose > 50 mg/m^2: alternative protocol[b] or reduce by 25 – 50%	CrCl 50 – 70 mL/min: reduce by 25%	Reduce by 25% or use carboplatin (if available)	GFR 50 – 59 mL/min: reduce by 25% Curative – GFR 40-49 mL/min: reduce by 50% Palliative – GFR < 50 mL/min: avoid	GFR 50 – 59 mL/min: reduce by 25% GFR 40 – 49 mL/min: reduce by 50%	Contraindicated in patients with serum creatinine levels > 200 µmol/L. Repeat courses are not advised until serum creatinine is < 140 µmol/L and/or blood urea < 9 mmol/L.
30 – 44	Avoid	CrCl 30 – 50 mL/min: reduce by 50%	Avoid or delay or use carboplatin (if available)	Curative – GFR < 40 mL/min: avoid	GFR < 40 mL/min: avoid	
15 – 29		Avoid		Avoid	Avoid	
< 15 (without KRT)						

Abbreviations: CrCl, creatinine clearance calculated using the Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease—Epidemiology Collaboration equation; GFR, glomerular filtration rate (not standarised to body surface area); KRT, kidney replacement therapy. a In patients with curative intent, good performance status and no concomitant nephrotoxic drugs. b In patients with either a poor performance status or concomitant nephrotoxic drugs.

Table 2: **Comparison of ADDIKD's recommendations vs existing guidance for cisplatin dosing according to kidney function.**

measures, and advocates for the use of directly measured GFR prior to the administration of high-dose cisplatin or where eGFR is unreliable (see Fig. 2 for 'practice points' for cisplatin). The latter includes patients with extremes of body composition, amputees, paraplegia, or conditions of skeletal muscle.[1] Measuring GFR in these circumstances prevents escalation of kidney-related adverse events in patients with reduced kidney function. Estimated kidney function values may underestimate true kidney function leading to unnecessary omission of cisplatin as a treatment option.

Carboplatin

Carboplatin is used in both oncological and haematological malignancies, with its dose calculation being directly reliant on actual kidney function. This is because carboplatin clearance is linearly proportional to kidney function, with elimination by the kidneys largely dependent on glomerular filtration rate and only a minor reliance on tubular secretion.[41,42] A strong correlation exists between carboplatin area under the curve (AUC), kidney function and the severity of thrombocytopenia, and, to a lesser extent, leucopoenia,[43–48] Therefore in contemporary practice the Calvert formula uses kidney function and AUC to calculate carboplatin doses, leading to less grade ≥ 3 myelosuppression (based on National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE])[49] whilst maintaining therapeutic efficacy in patients with eGFR < 60 mL/min/1.73 m^2.[44,50]

Besides regulatory-approved product information, existing guidelines recommend the Calvert formula (Table 3). ADDIKD did not recommend KDIGO CKD categories in guiding the dosing of carboplatin in reduced kidney function, but rather the use of the Calvert formula (see Supplementary Material 4 for ADDIKD's complete carboplatin dosing recommendations).[1]

There is inconsistency amongst existing guidelines given the heterogenous use of kidney function assessments applied to the Calvert formula, potentially creating significant variation in calculated doses.[51] ADDIKD proposes that directly measured GFR (not standardised to body surface area [BSA]) as the preferred kidney function value to be used to mirror the original Calvert formula study.[44] This ensures that with curative intent, or in clinical situations where estimated kidney function is unreliable (including eGFR > 125 mL/min/1.73 m^2 or ≤ 45 mL/min/1.73 m^2), directly measured GFR provides for more consistent therapeutic dosing.

The ADDIKD guideline acknowledges that access to and affordability of directly measured GFR can be unfeasible in some settings. In these situations where the decision is made to use estimated kidney function values instead of the gold standard directly measured GFR, the use of BSA-adjusted estimated GFR as the kidney function value in the Calvert formula is

Practice points

- For eGFR < 60 mL/min/1·73 m^2, to ensure therapeutic dosing and reduce the risk of a further decline in kidney function from cisplatin-induced adverse kidney events, directly measured GFR is preferred for initial dosing, especially where either:
  - cisplatin dose > 50 mg/m^2
  - eGFR is unreliable (e.g., extremes of body composition, amputees, paraplegia, conditions of skeletal muscle).
- To minimise the risk of cisplatin-induced adverse kidney events, adequate preventative and supportive care measures (as per local institutional policies) are advised for all patients receiving cisplatin. This includes maintaining adequate euvolemia, monitoring urine output through appropriate fluid hydration pre- and post-infusion, and preventing salt-wasting with magnesium and potassium supplementation.[43,49,50] Taking into account the scarcity of evidence, mannitol may be considered to further ameliorate the risk by promoting osmotic diuresis, especially in patients receiving ≥ 100 mg/m^2.[43,49] Monitor kidney function, fluid balance, electrolytes and albumin levels throughout treatment.
- The dose reduction applies to each individual dose within the treatment cycle. For a continuous infusion, the dose reduction refers to the total dose and not the total number of days or duration for the infusion per treatment cycle.

Fig. 2: Cisplatin dosing practice points from ADDIKD.[1]

eGFR (mL/min/1·73 m²)	ADDIKD[1]	eviQ[9]	BC Cancer[6]	Krens, *et al.*,[7] Giraud, *et al.*,[8]	Renal Drug Database[4]	Product Information[5]
≥ 60	Dose calculation based on mGFR[a] or BSA-adjusted eGFR and AUC using the Calvert formula	Dose calculation based on CrCl and AUC using the Calvert formula	Dose with mGFR from nuclear renogram or CrCl and AUC using the Calvert formula	Dose calculation based on kidney function and AUC using the Calvert formula	Dose calculation based on kidney function and AUC using the Calvert formula	Full dose (based on 400 mg/m²)
45 – 59	Dose calculation based on mGFR[a] or BSA-adjusted eGFR and AUC using the Calvert formula					
30 – 44						CrCl 20 – 39 mL/min: reduce to 250 mg/m²
15 – 29	Dose calculation based on mGFR and AUC using the Calvert formula					CrCl < 20: reduce to 150 mg/m²
< 15 (without KRT)	Consult MDT					

Abbreviations: AUC, area under the concentration–time curve; BSA-adjusted eGFR, body surface area adjusted estimated glomerular filtration rate via the Chronic Kidney Disease—Epidemiology Collaboration equation (mL/min); CrCl, creatinine clearance calculated using the Cockcroft–Gault equation; eGFR, estimated glomerular filtration rate via the Chronic Kidney Disease—Epidemiology Collaboration equation; MDT, multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing; mGFR, directly measured glomerular filtration rate (not standarised to body surface area, mL/min); KRT, kidney replacement therapy. a When either treatment intent is curative or patient has extremes of body composition, conditions of skeletal muscle, is an amputee or is paraplegic or eGFR > 125 mL/min/1.73 m² or eGFR ≤ 45 mL/min/1.73 m²

Table 3: **Comparison of ADDIKD's recommendations vs existing guidance for carboplatin dosing according to kidney function.**

recommended by expert clinical consensus. AUC calculated using eGFR (via the Chronic Kidney Disease—Epidemiology Collaboration [CKD-EPI] equation), when adjusted for an individual's BSA (calculated through either DuBois DuBois or Mosteller equations)[52,53] in the Calvert formula, is more accurate than AUC calculated using CrCl via the Cockcroft–Gault equation.[54–57] Since ADDIKD's publication, KDIGO's Clinical Practice Guideline for the Evaluation and Management of CKD,[58] Advanced Pharmacy Australia,[59] and the American Society of Onco-Nephrology[60] have supported the use of BSA-adjusted eGFR for carboplatin dose calculations over CrCl (when directly measured GFR is not feasible).

The change to BSA-adjusted eGFR was identified as a significant practice change, based on historical reliance on CrCl calculated by the Cockcroft–Gault equation. Furthermore, many internationally used oncology prescribing software packages employ CrCl as the default kidney function value in the Calvert formula.

To support networks yet to transition to electronic prescribing software and align with ADDIKD recommendations, eviQ (Cancer Institute NSW's web-based government program for point of care information for health professionals in Australia [www.eviq.org]) developed a 'rapid learning module' as an online educational learning tool for carboplatin dose calculation.[9] An online calculator for carboplatin dosing based on both directly measured GFR and BSA-adjusted eGFR was also developed.

In contrast to existing guidelines, ADDIKD incorporates additional practice-based recommendations to standardise approaches to calculation of carboplatin doses. This includes a recommendation against lowering target AUC in reduced kidney function, as it may compromise clinical benefit. The recalculation of carboplatin doses at each cycle was also deemed unnecessary, except when baseline kidney function (e.g., eGFR) alters by > 20% or when there is a change in the clinical status of the patient.[1]

Nivolumab

As a monoclonal antibody, nivolumab is not pharmacokinetically reliant on kidney function for drug elimination,[61–63] and has a low incidence of CTCAE grade ≥ 3 or treatment-limiting toxicities in patients with reduced kidney function.[64–71] Nivolumab illustrates that although an anticancer drug may appear safe at any level of kidney function, precautions still exist that should be considered on an individual patient level. As a newer anticancer immunotherapy agent, evidence of nivolumab tolerability in eGFR < 30 mL/min/1.73 m² is only now emerging. Immune-related adverse kidney events have been observed with nivolumab treatment, and commonly involve AKI, arising from acute interstitial nephritis, acute tubular injury, or glomerular diseases.[68,70,72–77]

The impact of reduced kidney function at baseline on the risk of immune-related adverse kidney events with nivolumab is uncertain, with some studies reporting no association[72,74,76,77] and another observing an increased risk of immune-checkpoint inhibitor-associated AKI with declining kidney function.[78] ADDIKD notes the developing toxicity data, especially as nivolumab use expands amongst wider patient populations, as well as in combination with nephrotoxic agents [refer to Appendix 5 of the ADDIKD guideline for a list of nephrotoxic anticancer drugs].[1]

Existing guidance does not recommend dose adjustments to nivolumab in the presence of reduced kidney function.[5–9] ADDIKD similarly does not suggest dose adjustments, however provides additional considerations for high-risk situations (e.g., kidney transplant recipients, patient groups susceptible to developing immune-related AKI) and monitoring for immune-related kidney events (see Supplementary Material 5 for ADDIKD's complete nivolumab dosing recommendations).[1]

In agreement with several international guidelines,[79,80] ADDIKD recommends assessment of baseline kidney function, and measurement of electrolyte levels and urinalysis before starting and as clinically indicated throughout nivolumab treatment to monitor for immune-related kidney events. This is pertinent in patients with additional risk factors for developing immune-related AKI (such as concomitant nephrotoxic drug exposure, combination immune checkpoint inhibitor therapy, dehydration, and pre-existing hypertension).[72,74,76–78]

The next steps for implementation of ADDIKD into clinical practice

These drug exemplars demonstrate how clinical decision-making for dosing patients with reduced kidney function can be standardised whilst accommodating individual patient and treatment-related factors. Compared to existing guidance, ADDIKD integrates evidence with clinical expertise to formulate a justified pragmatic dosing recommendation for individual drugs in the presence of reduced kidney function. It also provides a traffic-light colour-coded, easy to read, 'quick reference' dosing tables summarising guidance for multidisciplinary cancer teams (including members who are less familiar with anticancer drugs or treatment protocols). Although only 59 drugs were evaluated in ADDIKD, the methodology of assessment could be utilised by clinicians for other anticancer drugs in the future. Additionally, ADDIKD's integration into cancer treatment resources (i.e., eviQ, BC Cancer) and clinical trial protocols would aid in the global standardisation of anticancer drug dose adjustment in reduced kidney function.

Local 'change champions', from multiple disciplines (i.e., oncologists/haematologists, nephrologists, pharmacists, nurses), are imperative in leading the implementation of ADDIKD's principles—primarily using eGFR for estimated assessment, harmonising the categorisation of kidney function to KDIGO and application of the relevant dosing recommendations. We recommend that cancer practices employ a multidisciplinary team review of current policies and workflow processes. This could include an assessment of electronic prescribing system capabilities including the use of auto-calculation of carboplatin doses using the Calvert formula. Likewise, identifying which of their patients would benefit from a directly measured GFR assessment and determining local alternatives for kidney function assessment in such patients if directly measured GFR is impractical.

Local pathology service providers should be consulted to ensure eGFR is reported using the CKD-EPI equation. Additionally, directly measured GFR values should be reported appropriately as mL/min and not as a BSA standardised value.

Depending on local capacity, the adoption of ADDIKD in cancer centres should occur in a staged manner to allow for gradual familiarisation. One approach could include incorporating ADDIKD dosing recommendations for all drugs except for carboplatin. After a period of familiarisation, the cancer centre may wish to consider the major change of adopting BSA-adjusted eGFR for carboplatin prescribing (where directly measured GFR was not feasible). Ultimately, a 'lead by example' approach from institutional 'change champions' is required along with clear advocacy for the advantages ADDIKD can bring to the practice, building on the implementation of several major ADDIKD principles, completing pre and post implementation audits and recruiting the other members of the team to further develop dose optimising changes.

Outstanding questions

There are several ADDIKD limitations to consider during implementation and for future updates to the guideline. Firstly, stem cell mobilisation, bone marrow transplantation, cellular therapies and kidney replacement therapies were outside the scope of the guidance. These are highly complex areas with limited data and would benefit from a consensus guideline process as comprehensive as ADDIKD. Secondly, inclusion of newer drugs over time and updating existing guidance as new evidence emerges. The process of consensus building, and guideline development has been established, however the requirement for guideline continuity and updates in this rapidly evolving area in medicine is difficult without definitive resource commitment. The initial publication was through a government funded project and involved clinicians volunteering their expertise. Thirdly, inclusion of newer and more precise methods of kidney function estimation. For example, recently the utilisation of cystatin C-creatinine measured

estimation equations have been shown to be more accurate in clinical situations where eGFR is unreliable.[58]

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Data sharing statement

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103161.

References

1 Sandhu G, Adattini J, Gordon EA, O'Neill N, On behalf of the ADDIKD Guideline Working Group. International consensus guideline on anticancer drug dosing in kidney dysfunction. https://www.eviq.org.au/clinical-resources/addikd-guideline/4174-anticancer-drug-dosing-in-kidney-dysfunction; 2022. Accessed July 31, 2024.
2 Sandhu G, Adattini J, Gordon EA, et al. Aligning kidney function assessment in patients with cancer to global practices in internal medicine. *eClinicalMedicine*. 2025;82:103102.
3 Sandhu G, Gordon EA, Adattini J, et al. A methodology for determining dosing recommendations for anticancer drugs in patients with reduced kidney function. *eClinicalMedicine*. 2025;82:103101.
4 Ashley C, Dunleavy A. The renal drug database. https://renaldrugdatabase.com/. Accessed April 1, 2024.
5 Therapeutic goods administration. https://www.ebs.tga.gov.au.
6 BC Cancer. Cancer drug manual. http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual; 2022. Accessed April 1, 2022.
7 Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*. 2019;20(4):e200–e207.
8 Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. *Lancet Oncol*. 2023;24(6):e229.
9 eviQ cancer treatments online. https://www.eviq.org.au/; 2023. Accessed May 8, 2023.
10 Treon SP, Chabner BA. Concepts in use of high-dose methotrexate therapy. *Clin Chem*. 1996;42(8 Pt 2):1322–1329.
11 Schmiegelow K. Advances in individual prediction of methotrexate toxicity: a review. *Br J Haematol*. 2009;146(5):489–503.
12 Levêque D, Becker G, Toussaint E, Fornecker L-M, Paillard C. Clinical pharmacokinetics of methotrexate in oncology. *Int J Pharmacokinetics*. 2017;2(2):137–147.
13 Joerger M, Huitema AD, van den Bongard HJ, et al. Determinants of the elimination of methotrexate and 7-hydroxy-methotrexate following high-dose infusional therapy to cancer patients. *Br J Clin Pharmacol*. 2006;62(1):71–80.
14 Kawakatsu S, Nikanjam M, Lin M, et al. Population pharmacokinetic analysis of high-dose methotrexate in pediatric and adult oncology patients. *Cancer Chemother Pharmacol*. 2019;84(6):1339–1348.

15 Malyszko J, Lee MW, Capasso G, et al. How to assess kidney function in oncology patients. *Kidney Int*. 2020;97(5):894–903.
16 Stefani M, Singer RF, Roberts DM. How to adjust drug doses in chronic kidney disease. *Aust Prescr*. 2019;42(5):163–167.
17 Ferreri AJ, Guerra E, Regazzi M, et al. Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. *Br J Cancer*. 2004;90(2):353–358.
18 McKay P, Wilson MR, Chaganti S, Smith J, Fox CP, Cwynarski K. The prevention of central nervous system relapse in diffuse large B-cell lymphoma: a British Society for Haematology good practice paper. *Br J Haematol*. 2020;190(5):708–714.
19 Zhu JJ, Gerstner ER, Engler DA, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. *Neuro Oncol*. 2009;11(2):211–215.
20 Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004;101(12):2788–2801.
21 Beex LV, Hermus AR, Pieters GF, van Hoesel QG, Nooy MA, Mignolet F. Dose intensity of chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil in the elderly with advanced breast cancer. *Eur J Cancer*. 1992;28(2-3):686–690.
22 Gelman RS, Taylor SG 4th. Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: the elimination of age trends in toxicity by using doses based on creatinine clearance. *J Clin Oncol*. 1984;2(12):1404–1413.
23 Lichtman SM, Cirrincione CT, Hurria A, et al. Effect of pretreatment renal function on treatment and clinical outcomes in the adjuvant treatment of older women with breast cancer: alliance A171201, an Ancillary Study of CALGB/CTSU 49907. *J Clin Oncol*. 2016;34(7):699–705.
24 Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. *Toxins*. 2010;2(11):2490–2518.
25 Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. *J Nephrol*. 2018;31(1):15–25.
26 Hrushesky WJ, Shimp W, Kennedy BJ. Lack of age-dependent cisplatin nephrotoxicity. *Am J Med*. 1984;76(4):579–584.
27 Reece PA, Stafford I, Russell J, Gill PG. Reduced ability to clear ultrafilterable platinum with repeated courses of cisplatin. *J Clin Oncol*. 1986;4(9):1392–1398.
28 Vermorken JB, van der Vijgh WJ, Klein I, et al. Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. *Clin Pharmacol Ther*. 1986;39(2):136–144.
29 Ichioka D, Miyazaki J, Inoue T, et al. Impact of renal function of patients with advanced urothelial cancer on eligibility for first-line chemotherapy and treatment outcomes. *Jpn J Clin Oncol*. 2015;45(9):867–873.
30 Koshkin VS, Barata PC, Rybicki LA, et al. Feasibility of cisplatin-based neoadjuvant chemotherapy in muscle-invasive bladder cancer patients with diminished renal function. *Clin Genitourin Cancer*. 2018;16(4):e879–e892.
31 Talley R, Boutseleis J, Neidhart JA. Cis-platinum plus high-dose methotrexate. Toxicity and efficacy in ovarian carcinoma. *Am J Clin Oncol*. 1983;6(3):369–374.
32 Kidera Y, Kawakami H, Sakiyama T, et al. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection. *PLoS One*. 2014;9(7):e101902.
33 Liu JQ, Cai GY, Wang SY, et al. The characteristics and risk factors for cisplatin-induced acute kidney injury in the elderly. *Ther Clin Risk Manag*. 2018;14:1279–1285.
34 Lagrange JL, Médecin B, Etienne MC, et al. Cisplatin nephrotoxicity: a multivariate analysis of potential predisposing factors. *Pharmacotherapy*. 1997;17(6):1246–1253.
35 Morgan KP, Snavely AC, Wind LS, et al. Rates of renal toxicity in cancer patients receiving cisplatin with and without mannitol. *Ann Pharmacother*. 2014;48(7):863–869.
36 Motwani SS, McMahon GM, Humphreys BD, Partridge AH, Waikar SS, Curhan GC. Development and validation of a risk prediction model for acute kidney injury after the first course of cisplatin. *J Clin Oncol*. 2018;36(7):682–688.
37 Reece PA, Stafford I, Davy M, Freeman S. Disposition of unchanged cisplatin in patients with ovarian cancer. *Clin Pharmacol Ther*. 1987;42(3):320–325.
38 Jiang DM, Gupta S, Kitchlu A, et al. Defining cisplatin eligibility in patients with muscle-invasive bladder cancer. *Nat Rev Urol*. 2021;18(2):104–114.
39 Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(3):244–258.
40 Lelli G, Melotti B, Pannuti F, et al. Chemotherapy with cisplatin, epirubicin, methotrexate in the treatment of locally advanced or metastatic transitional cell cancer of the bladder (TCC). *J Chemother*. 1992;4(4):239–243.
41 Oguri S, Sakakibara T, Mase H, et al. Clinical pharmacokinetics of carboplatin. *J Clin Pharmacol*. 1988;28(3):208–215.
42 Van Echo DA, Egorin MJ, Whitacre MY, Olman EA, Aisner J. Phase I clinical and pharmacologic trial of carboplatin daily for 5 days. *Cancer Treat Rep*. 1984;68(9):1103–1114.
43 Colombo N, Speyer JL, Green M, et al. Phase II study of carboplatin in recurrent ovarian cancer: severe hematologic toxicity in previously treated patients. *Cancer Chemother Pharmacol*. 1989;23(5):323–328.
44 Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7(11):1748–1756.
45 Jodrell DI, Egorin MJ, Canetta RM, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol*. 1992;10(4):520–528.
46 Schmitt A, Gladieff L, Laffont CM, et al. Factors for hematopoietic toxicity of carboplatin: refining the targeting of carboplatin systemic exposure. *J Clin Oncol*. 2010;28(30):4568–4574.
47 Speyer JL, Sorich J. Intraperitoneal carboplatin: rationale and experience. *Semin Oncol*. 1992;19(1 Suppl 2):107–113.
48 van Glabbeke M, Renard J, Pinedo HM, et al. Iproplatin and carboplatin induced toxicities: overview of phase II clinical trial conducted by the EORTC Early Clinical Trials Cooperative Group (ECTG). *Eur J Cancer Clin Oncol*. 1988;24(2):255–262.
49 *National Cancer Institute Common Terminology Criteria for Adverse Events: (CTCAE)*. National Institutes of Health, National Cancer Institute; 2017.
50 Oguri T, Shimokata T, Ito I, et al. Extension of the Calvert formula to patients with severe renal insufficiency. *Cancer Chemother Pharmacol*. 2015;76(1):53–59.
51 Akgül S, Chan BA, Manders PM. Carboplatin dose calculations for patients with lung cancer: significant dose differences found depending on dosing equation choice. *BMC Cancer*. 2022;22(1):829.
52 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317(17):1098.
53 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989;5(5):303–311.
54 McLean L, Whittle JR, Graham J, et al. Carboplatin dosing in the era of IDMS-creatinine; the Cockroft-Gault formula no longer provides a sufficiently accurate estimate of glomerular filtration rate for routine use in clinical care. *Gynecol Oncol*. 2020;157(3):793–798.
55 Janowitz T, Williams EH, Marshall A, et al. New model for estimating glomerular filtration rate in patients with cancer. *J Clin Oncol*. 2017;35(24):2798–2805.
56 Beumer JH, Inker LA, Levey AS. Improving carboplatin dosing based on estimated GFR. *Am J Kidney Dis*. 2018;71(2):163–165.
57 Tsang C, Akbari A, Frechette D, Brown PA. Accurate determination of glomerular filtration rate in adults for carboplatin dosing: moving beyond Cockcroft and Gault. *J Oncol Pharm Pract*. 2021;27(2):368–375.
58 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2024;105:S117–S314.
59 Mirkov S, Scuderi C, Lloyd J, et al. Estimation of kidney function for medication dosing in adult patients with chronic kidney disease: a practice update. *J Pharm Pract Res*. 2024;54(1):94–106.
60 Kitchlu A, Silva VTCE, Anand S, et al. Assessment of GFR in patients with cancer: a statement from the American society of Onconephrology. *Clin J Am Soc Nephrol*. 2024;19(8):1061–1072.
61 Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):58–66.
62 Hurkmans DP, Basak EA, van Dijk T, et al. A prospective cohort study on the pharmacokinetics of nivolumab in metastatic non-small cell lung cancer, melanoma, and renal cell cancer patients. *J Immunother Cancer*. 2019;7(1):192.
63 Kato R, Ikarashi D, Matsuura T, et al. Analyses of nivolumab exposure and clinical safety between 3-mg/kg dosing and 240-mg

flat dosing in Asian patients with advanced renal cell carcinoma in the real-world clinical setting. *Transl Oncol*. 2020;13(6):100771.
64 Ansari J, Ali M, Farrag A, Ali AM, Alhamad A. Efficacy of nivolumab in a patient with metastatic renal cell carcinoma and end-stage renal disease on dialysis: case report and literature review. *Case Reports Immunol*. 2018;2018:1623957.
65 Jain J, Stein J, Garje R. Evaluation of checkpoint inhibitors in cancer patients with end-stage renal disease on hemodialysis: case series and review of the literature. *J Immunother*. 2020;43(8):244–249.
66 Kanz BA, Pollack MH, Johnpulle R, et al. Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal, or hepatic dysfunction. *J Immunother Cancer*. 2016;4:60.
67 Fernandez-Diaz AB, Cunquero-Tomas AJ, Garcia-Medina A, Ferrer-Guillen B, Berrocal A. Are patients in haemodialysis good candidates for immunotherapy treatment? *Melanoma Res*. 2019;29(5):553–555.
68 Kitchlu A, Jhaveri KD, Sprangers B, Yanagita M, Wanchoo R. Immune checkpoint inhibitor use in patients with end-stage kidney disease: an analysis of reported cases and literature review. *Clin Kidney J*. 2021;14(9):2012–2022.
69 Osmán-García I, Congregado-Ruiz CB, Lendínez-Cano G, Baena-Villamarin C, Conde-Sanchez JM, Medina-López RA. Outcomes and safety of biweekly and monthly nivolumab in patients with metastatic renal cell carcinoma and dialysis: three case reports and literature review. *Urol Int*. 2020;104(3-4):323–326.
70 Tachibana H, Kondo T, Ishihara H, Takagi T, Tanabe K. Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma and end-stage renal disease at 2 centers. *Clin Genitourin Cancer*. 2019;17(4):e772–e778.
71 Vitale MG, Baldessari C, Milella M, et al. Immunotherapy in dialysis-dependent cancer patients: our experience in patients with metastatic renal cell carcinoma and a review of the literature. *Clin Genitourin Cancer*. 2019;17(5):e903–e908.
72 Chute DF, Zhao S, Strohbehn IA, et al. Incidence and predictors of CKD and estimated GFR decline in patients receiving immune checkpoint inhibitors. *Am J Kidney Dis*. 2022;79(1):134–137.
73 Kitchlu A, Jhaveri KD, Wadhwani S, et al. A systematic review of immune checkpoint inhibitor-associated glomerular disease. *Kidney Int Rep*. 2021;6(1):66–77.
74 Koks MS, Ocak G, Suelmann BBM, et al. Immune checkpoint inhibitor-associated acute kidney injury and mortality: an observational study. *PLoS One*. 2021;16(6):e0252978.
75 Manohar S, Kompotiatis P, Thongprayoon C, Cheungpasitporn W, Herrmann J, Herrmann SM. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. *Nephrol Dial Transplant*. 2019;34(1):108–117.
76 Meraz-Muñoz A, Amir E, Ng P, et al. Acute kidney injury associated with immune checkpoint inhibitor therapy: incidence, risk factors and outcomes. *J Immunother Cancer*. 2020;8(1):e000467.
77 Seethapathy H, Zhao S, Chute DF, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clin J Am Soc Nephrol*. 2019;14(12):1692–1700.
78 Cortazar FB, Kibbelaar ZA, Glezerman IG, et al. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. *J Am Soc Nephrol*. 2020;31(2):435–446.
79 Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline Update. *J Clin Oncol*. 2021;39(36):4073–4126.
80 Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer*. 2021;9(6):e002435.