Guideline for management of hydration during systemic anti-cancer therapy containing cisplatin

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1. Background

1.1. Nephrotoxicity is a major dose-limiting side effect of cisplatin. The kidney accumulates cisplatin to a greater degree than other organs and is the major route for its excretion.

1.2. The cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration. The disproportionate accumulation of cisplatin in kidney tissue contributes to cisplatin-induced nephrotoxicity.

1.3. Cisplatin nephrotoxicity can present in several ways including hypomagnesaemia and other electrolyte disturbances, Fanconi-like syndrome, anaemia, thrombotic microangiopathy, increased serum creatinine and urea. However, the most serious and one of the more common presentations is acute kidney injury (AKI) which occurs in 20–30% of patients. (Perazella et al 2022)

1.4. Typically, the onset of renal toxicity begins several days after the dose of cisplatin. The urine output is usually preserved, and the urine may contain glucose and small amounts of protein. Recovery of renal function usually occurs over a period of 2–4 weeks, although progressive and permanent nephrotoxicity can result with successive treatment courses despite preventative measures.

2. Scope

2.1. There is no standard fluid hydration schedule for cisplatin administration, and schedules vary significantly across the UK. Hydration schedules should consider the following conditions for the patient; adequate renal function, adequate hydration prior to administration of cisplatin, no contraindication to saline loading (e.g., uncompensated cardiac conditions), and ability to comply with recommended oral hydration protocol, or expectation that volume status can be maintained (e.g., with fluids via enteral feeding tube or IV).

2.2. The purpose of this protocol is to standardise hydration schedules and administration of cisplatin chemotherapy for adult patients across Wales. The hydration schedules are based on the available evidence and standard practice in other cancer centres across the UK.

3. Risk Factors for Cisplatin-Induced Nephrotoxicity

3.1. Risk factors that make some patients more susceptible to cisplatin induced nephrotoxicity include:

3.1.1. Higher Dose of Cisplatin
3.1.2. Increased frequency of treatment
3.1.3. High cumulative doses
3.1.4. Other nephrotoxic medicines e.g., NSAIDs, aminoglycosides
3.1.5. Female sex
3.1.6. Age (the risk is higher in older patients)
3.1.7. Smoking
3.1.8. Hypoalbuminaemia
3.1.9. Pre-existing renal insufficiency (limited data in humans)

4. Prevention of Cisplatin-induced nephrotoxicity

4.1. Despite the recent advances in understanding the mechanism of cisplatin–induced nephrotoxicity, prevention still relies on drug dosage decrease, specific measures of hydration, and active screening for renal abnormalities as part of the pre-chemotherapy assessment.

4.2. Good hydration and urine output prevents retention of cisplatin in the kidneys and is essential for minimising damage in the kidneys. Approximately 80% of cisplatin is excreted within 24 hours of administration, therefore hydration should continue for this period.

4.3. Oral post-hydration has been proven to be as safe as intravenous post-hydration in patients with Cisplatin doses of <60mg/m^2 (Horinouchi et al 2018 and Puisset et al 2019). As a result, oral hydration is incorporated into this guidance for lower doses of cisplatin.

4.4. Although many hydration regimens include the use of either mannitol or furosemide, there is no good evidence that diuretics provide any added benefit. Recently, a randomized trial demonstrated that sodium chloride 0.9% alone or with furosemide provides better renal protection than sodium chloride 0.9% plus mannitol (Santoso et al, Launay-Vacher et al). There may also be some benefit of mannitol in high doses of cisplatin, but the evidence is not compelling (Perazella et al). Mannitol also causes more nausea and vomiting and, in patients with diabetes or hypertension, can lead to deterioration in renal function (Songtao Li et al).

Hence on balance, and given the practical challenges of its use, mannitol has been removed from the recommended hydration schedules in this guideline.

4.5. Cisplatin and magnesium affect the same sodium and water channels in the outer medulla. Cisplatin induces magnesium depletion, and magnesium deficiency itself may enhance cisplatin nephrotoxicity.

Cisplatin treatment often produces extensive gastrointestinal side effects, which might lead to more magnesium depletion through anorexia and diarrhoea. Eventually, patients with these side effects may become more susceptible to the nephrotoxicity of cisplatin.

Hypomagnesaemia should be managed (as guided by local policy) prior to and during treatment with cisplatin. There is robust evidence that this reduces the incidence of cisplatin-induced nephrotoxicity. Serum magnesium levels should be monitored routinely in patients receiving cisplatin chemotherapy.

5. Practical Considerations

5.1. **Prior to prescribing of Cisplatin-Containing SACT**

5.1.1. Review toxicity of any previous dose(s) of cisplatin and take account of previous renal impairment when making decisions about subsequent doses.

5.1.2. The use of cisplatin in patients with pre-existing renal impairment must be carefully considered. Alternatives should be considered, where available, for patients with GFR <45mL/min. The table below provides general guidelines for dosing in renal impairment, however, refer to individual SACT protocol for specific recommendations.

GFR (mL/min)	Dose
≥60	100%
45-59	75%
<45	Consider alternative
Cockcroft - Gault formula	
Male patients:	$\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$
Female patients:	$\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

5.2. **Prior to attendance for cisplatin-containing SACT**

5.2.1. Inform the patient of the importance of drinking 2 litres (4 pints) of clear fluid over the 24 hours prior to, and 24 hours after chemotherapy – provide verbal and written information
5.2.2. Check FBC, U&E (including magnesium, potassium) and albumin
5.2.3. Patients with low magnesium (hypomagnesaemia) may require supplementation between cycles (as guided by local policy)
5.2.4. Patients with low potassium (hypokalaemia) may require supplementation between cycles (as guided by local policy)
5.2.5. Calculate the creatinine clearance using the Cockroft-Gault formula
5.2.6. Additional premedication with Furosemide may be appropriate in certain patient groups e.g. cardiac failure.

5.3. On arrival for cisplatin-containing SACT

5.3.1. Weigh the patient on arrival
5.3.2. Check the patient has been able to drink 2 litres of fluid in the last 24 hours and is passing good volumes of urine.
5.3.3. If any concerns about fluid intake or urine output in the last 24 hours seek advice from a clinician
5.3.4. Ensure access to a supply of drinking water and advise to drink plenty throughout the day

5.4. Target Hydration Schedules

5.4.1. Refer to Section 6

5.5. Monitoring during cisplatin-containing SACT

5.5.1. Monitor how often the patient passes urine throughout chemotherapy.
5.5.2. At the end of IV fluids, weigh the patient. If they have gained >2kg, they should be given furosemide 20mg orally. For practical reasons and to prevent delay, this should be built into SACT protocols as an ‘as required’ medicine.
5.5.3. If the patient does not pass urine within 30-60 minutes of furosemide or there are any symptoms of fluid overload (new or worsening shortness of breath, swollen ankles, abdominal bloating) they will need a clinical review prior to discharge.
5.5.4. For multi-day (including inpatient) regimens, weigh the patient at the start of each treatment day, following guidance in 5.5.2 if they have gained >2kg. It is not necessary to weigh at the end of the day, but obtain medical review if there are any obvious signs of fluid overload such as new onset breathlessness, fullness in the abdomen or swollen ankles.

5.6. **Dose modification for renal impairment**

5.6.1. Review the toxicity of previous dose of cisplatin and take account of previous renal impairment when making decision about subsequent doses. The table in section 5.1.2 may be used as a general guide for dose modification.

6. Suggested Hydration Schedules

Cisplatin dose mg/m^2	**Pre-hydration**	**Cisplatin**	**Post-hydration**	**Total Fluid Volume**
≥80	1000mL Sodium Chloride 0.9% with 20mmol Potassium and 10mmol Magnesium IV over 2 hours	Cisplatin in 1000mL Sodium Chloride 0.9% IV over 2 hours	1000mL Sodium Chloride 0.9% with 20mmol Potassium and 10mmol Magnesium IV over 2 hours	3000mL
61-79	1000mL Sodium Chloride 0.9% with 20mmol Potassium IV over 1 hour	Cisplatin in 1000mL Sodium Chloride 0.9% IV over 2 hours	1000mL Sodium Chloride 0.9% with 20mmol Potassium and 10mmol Magnesium IV over 2 hours	3000mL
41-60	500mL Sodium Chloride 0.9% IV over 30 minutes	Cisplatin in 1000mL Sodium Chloride 0.9% IV over 2 hours	1000mL Sodium Chloride 0.9% with 20mmol Potassium and 10mmol Magnesium IV over 2 hours	2500mL
≤40	500mL Sodium Chloride 0.9% IV over 30 minutes	Cisplatin in 1000mL 0.9% Sodium Chloride IV over 1 hour	Patient required to drink 500mL before discharge	2000mL
	Note: this regimen does not supplement magnesium. Monitor and manage as guided by local policy.			

6.1. If another drug is being given in the regimen e.g. Etoposide in 1000mL Sodium Chloride 0.9%, then this may be used as part of the hydration schedule, provided the total fluid volume is equivalent to the total recommended hydration volume.

In this situation, the supplementation of electrolytes may also be affected; this should be reviewed and managed as guided by local policy.

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