Reducing pre- and post-hydration for cisplatin chemotherapy

The Dutch NVMO Committee for Sustainability and Efficiency has formulated recommendations to standardize the hydration protocol for cisplatin. The goal is to save both time and materials used without increasing the risk of nephrotoxicity.

Introduction

Cisplatin is used for many different malignancies. The most common dose-limiting toxicity is nephrotoxicity, manifesting as an increase in serum creatinine and electrolyte disturbances such as hypomagnesemia and hypokalemia. Hydration before and after cisplatin administration reduces the risk of nephrotoxicity by maintaining sufficient urine output. Hydration protocols for cisplatin are not standardized in national or international guidelines. When conducting a trial with cisplatin, it is almost always recommended to adhere to the institutional protocol for hydration. The basis for this cisplatin hydration recommendation is the systematic review published in *The Oncologist*.

Duration and Volume of the Hydration Protocol

Many studies have been published on the duration and/or volume of hydration protocols and the risk of nephrotoxicity. Most studies investigated other variables besides hydration duration and volume. In the Dutch retrospective cohort study by Niggebrugge-Mentink et al. describing non-small cell lung cancer patients, bias was considered to be limited since important variables were considered during patient selection. This study showed less nephrotoxicity when a short hydration protocol was applied (1 L prehydration infusion fluid in 2 hours + cisplatin in 1 L infusion fluid + 1 L post-hydration infusion fluid in 2 hours) as compared to a long hydration protocol. Prehydration with 1 L sodium chloride (NaCl) 0.9% in 1 hour prior to administration of chemotherapy (in the setting of chemoradiation therapy for patients with non-small cell lung cancer) was also shown to reduce the incidence of renal function deterioration compared to a longer schedule. Based on the systematic review, including the above studies, it can be concluded that a short protocol is safe or even safer than a long hydration protocol. There is insufficient data to support converting intraveneous prehydration to oral administration.

Composition of Hydration Fluid

There are no comparative studies between hydration with NaCl 0.9% and glucose-containing infusion fluids. The Summary of Product Characteristics (SmPC) and the European Society of Clinical Pharmacy (ESCP) recommend using NaCl 0.9% for hydration. Hypomagnesemia occurs in 1-10 percent of patients after cisplatin treatment according to the SmPC. All studies with magnesium supplementation showed that adding magnesium significantly reduced the incidence of nephrotoxicity. The amounts of magnesium supplementation ranged from 8 mEq (97 mg) to 20 mEq (243 mg) of magnesium per cisplatin administration, with magnesium sulfate (MgSO4) being commonly used and no differences found between the various schedules. Hypokalemia also occurs in 1-10 percent of patients after cisplatin treatment

according to the SmPC. Based on the literature found, it cannot be concluded whether potassium supplementation influences the incidence of nephrotoxicity. Since hypokalemia is observed clinically, supplementation is often given to prevent this. Doses used in studies varied and included 10 mmol to 80 mmol of potassium chloride (KCl) per cisplatin administration.

Diuretics

Diuretics could accelerate the elimination of cisplatin, thereby reducing nephrotoxicity. A meta-analysis concluded that mannitol is safe and effective in preventing cisplatin-induced nephrotoxicity (particularly grade 3). Therefore, mannitol may be considered for high doses (≥ 100 mg/m²) of cisplatin. A recent study comparing furosemide with mannitol after cisplatin administration found no differences in creatinine change. From a practical standpoint and based on extensive experience with furosemide, it is preferred to use this drug, either as standard practice or after weight gain due to hydration fluid.

Infusion Rate of Cisplatin

The SmPC indicates a long infusion duration of 6-8 hours, but many hospitals administer this in 2-3 hours (or even shorter for lower doses). Pharmacokinetic studies find a correlation between peak levels and nephrotoxicity. Studies have been conducted where cisplatin was administered over 1 hour. There was no difference in nephrotoxicity between infusion times of 1 and 3 hours, but nausea and vomiting appeared to occur more frequently at higher infusion rates (1 vs. 8 hours). Based on the current literatue, no advice can be given regarding the optimal infusion time.

Recommendation for Hydration Protocol with Cisplatin

Cisplatin Dose	**Duration + Volume Prehydration**	**Duration + Volume Posthydration**	**Other**
6 mg/m²	1 L NaCl 0.9% in 1 hour	-	-
> 6 mg/m² and < 100 mg/m²	1 L HF in 2 hours	1 L HF in 2 hours if cisplatin in 1000 ml	consider furosemide
Head and neck tumors* > 6 mg/m² and < 100 mg/m²	1 L HF in 2 hours + 1 L NaCl 0.9% extra	1 L HF in 2 hours if cisplatin in 1000 ml	consider furosemide
≥ 100 mg/m²	1 L HF in 2 hours + 1 L NaCl 0.9% extra	2 L HF in 4 hours	consider furosemide

HF: hydration fluid harmonized composition: 1 L NaCl 0.9% + 15 g MgSO4 + 10 mmol KCl. Range for deviation: 1 L NaCl 0.9% + 1-25 g MgSO4 + ≤ 20 mmol KCl. NaCl: sodium chloride; MgSO4: magnesium sulfate; KCl: potassium chloride.. Head and neck patients are often less well-hydrated; therefore, pragmatically administer more fluid. Preference to give cisplatin in 1 L. If cisplatin in 500 ml, compensate with extra fluid. Low-threshold furosemide: e.g., use furosemide for overhydration (+ 2-3 kg compared to starting weight 20 mg furosemide orally + > 3-5 kg compared to starting weight 40 mg furosemide orally; weigh during posthydration or thereafter).

Recommendation

The recommendation is presented in the table. A distinction is made between three dosage ranges, with separate advice for head and neck tumors. Due to very limited research on continuous cisplatin infusion (e.g., R-DHAP), this group is excluded from this advice. In case of evident dehydration, consider more prehydration. Advise patients to adhere to a high oral fluid intake on the days surrounding the cisplatin administration.

Regarding the hydration fluid, a harmonized composition is recommended: 1 L NaCl 0.9% + 15 g MgSO4 + 10 mmol KCl. The range for deviation from this is: 1 L NaCl 0.9% + 1-25 g MgSO4 + ≤ 20 mmol KCl. Dutch large-scale producers were informed and had no objections to this composition. Use the same infusion fluid for prehydration and posthydration. Furosemide (standard or based on weight gain) can be used at all cisplatin doses. Mannitol can be considered for high doses (≥ 100 mg/m²) of cisplatin.

About the Authors:

The committee "sustainability and efficiency" of the Dutch Society of Medical Oncology (NVMO) was initiated in 2022. Their remit is to demonstrate that it is possible to increase both the sustainability as well as the efficiency of medical oncology care. The committee consists of medical oncologists and hospital pharmacists. They regularly publish specific guidelines and suggestions for daily practice based on both published literature and daily experience. All published guidelines are freely accessible at "https:www.nvmo.org/duurzaam-en-doelmatigheid/".

Current committee members (alphabetical order): Annemarie Becker ; Jeroen M.A Hendrikx; Anniek Goosens; Bregtje. Hermans; Mathilde Jalving; Roelof van Leeuwen; Maartje Los, Matthijs van de Poll; Gabe Sonke; Annelieke Willemsen; Machteld Wymenga; Michiel Zietse.

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