

# Nephrotoxicity

## Evidence in patients receiving cisplatin therapy

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**BACKGROUND:** Cisplatin has been used as a chemotherapeutic agent to treat many different cancers. A well-known side effect of cisplatin is nephrotoxicity, which is the primary dose-limiting toxicity. Hydration in conjunction with appropriate diuresis can decrease the incidence of nephrotoxicity.

**OBJECTIVES:** This article aims to identify best practices in supportive therapy for patients receiving cisplatin therapy.

**METHODS:** A team was assembled to review research-based evidence and summarize recommendations to address appropriate hydration regimens and forced diuresis for patients receiving cisplatin chemotherapy.

**FINDINGS:** After a systematic search of the literature, only one pediatric study was found. The remaining 22 research-based studies of adults were synthesized and critically appraised. Hydration is necessary to prevent nephrotoxicity with cisplatin administration. In addition, the administration of magnesium and mannitol may assist in maintaining renal function and reducing nephrotoxicity in adults receiving cisplatin. Additional research is needed to evaluate outcomes of these interventions in the pediatric population.

### KEYWORDS

cisplatin; hydration; nephrotoxicity; cancer; mannitol; magnesium

### DIGITAL OBJECT IDENTIFIER

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**CISPLATIN IS A PLATINUM COMPOUND THAT HAS BEEN USED** as a chemotherapeutic agent for many different cancers, including ovarian, testicular, lung, cervical, and bladder cancers (Ruggiero, Rizzo, Trombatore, Maurizi, & Riccardi, 2016; Santoso, Lucci, Coleman, Shafer, & Hannigan, 2003). The primary dose-limiting toxicity of cisplatin is nephrotoxicity, a well-known side effect (Jones, Spunt, Green, & Springate, 2008; Miller, Tadagavadi, Ramesh, & Reeves, 2010). Nephrotoxicity involves glomerular or tubular dysfunction of the kidneys after exposure to medications, other treatments, or toxins (Skinner, 2011). Nephrotoxicity associated with cisplatin is related to accumulation of metabolites in the renal proximal tubule cells of the kidneys, where about 90% of cisplatin undergoes urinary excretion (Ruggiero et al., 2016). Accumulation of these metabolites causes direct inflammation; the production of reactive oxygen species, which leads to oxidative cell damage; and cell death (Miller et al., 2010; Ruggiero et al., 2016). Many methods are available to measure kidney function and define nephrotoxicity or acute kidney injury (see Table 1).

Most patients receiving cisplatin experience acute impairment of glomerular and tubular function in varying degrees. Toxicity is dependent on individual cisplatin pharmacokinetics and is usually more severe with high total cisplatin doses and when other potential nephrotoxic medications are given concurrently (Skinner, 2011; Womer, Pritchard, & Barratt, 1985). In one study, children aged 10 years or older at treatment had a lower glomerular filtration rate 10 years after therapy compared to children aged younger than 10 years at treatment (Skinner et al., 2009).

Nephrotoxicity can be reversible, but for some individuals, it can result in permanent kidney injury, chronic progressive renal failure, or renal tubule function impairment (Skinner et al., 2009). Chronic and severe reductions of renal function have several sequelae. The immediate impact may be dose reduction or cessation of potentially lifesaving nephrotoxic chemotherapy, thereby increasing the risk of relapse or progression of the cancer. In the event of a disease relapse or progression, changes to renal function may limit enrollment in phase 1 or 2 clinical trials because of inclusion parameters related to baseline renal function.

Hydration and diuretics have been used in conjunction with cisplatin administration for decades to improve the excretion of cisplatin and reduce the incidence of nephrotoxicity. One method of promoting this excretion is through osmotic diuresis with mannitol (Morgan et al., 2014). However, the amount of hydration, the infusion time for hydration, and the use of diuretics vary among treatment protocols. The optimal hydration and diuretic regimen necessary to prevent cisplatin nephrotoxicity is unknown.