JNMS Journal of Nippon Medical School https://www.nms.ac.jp/sh/jnms/

## Letter to the Editor

# Comment on "Phase II Study of Short Hydration without Diuretics for Cisplatin-Based Chemotherapy"

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*To the Editor:*

We read a prospective phase II study by Wako et al.[1], which investigated short hydration without diuretics for cisplatin-based chemotherapy in patients with thoracic malignancies, with great interest.

The use of diuretics in cisplatin hydration regimens remains controversial, with systematic reviews showing conflicting conclusions regarding the utility of mannitol[2,3]. In addition, few studies have specifically reported the renoprotective effects of short hydration without diuretics. In this study, the authors found that 97.3% (36/37) of patients who received cisplatin-based regimen (dose: ≥60 mg/m2) without immune checkpoint inhibitor experienced no grade 2 or higher creatinine elevation during the first cycle, and 91.9% (34/37) did throughout all cycles, while 28.3% (13/46) of all patients required additional intravenous hydration on days other than cisplatin administration. These results are comparable with those of previous Japanese studies that used diuretics, suggesting that short hydration without diuretics can preserve renal function.

However, several critical limitations need to be addressed. First, this study lacked key patient background information. While it has been reported that age, sex, diabetes mellitus, liver dysfunction, pre-existing chronic kidney disease, alcohol ingestion, concomitant nephrotoxins (notably non-steroidal anti-inflammatory drugs), and nutritional status, including serum albumin, are risk factors for cisplatin-induced renal dysfunction[4], concomitant non-steroidal anti-inflammatory drug use and serum albumin levels were not described in this study. Second, standardized oral hydration guidance were not specified in this study. The feasibility of short hydration relies on the use of modern antiemetics and adequate oral fluid intake before and after cisplatin administration. For reproducibility and proper interpretation of the results, explicit documentation of oral hydration instructions given to patients is essential. Third, the timing of creatinine measurements was not specified in this study. Cisplatin-induced nephrotoxicity typically occurs 5–7 days after administration and resolves within several weeks[5]. Without a clearly defined measurement timing, this endpoint becomes vulnerable to variability. Fourth, the primary endpoint, the proportion of patients without grade 2 or higher creatinine elevation during the first cycle, is not a validated surrogate for clinically relevant outcomes, while this endpoint is pragmatic for the heterogeneous patient population with various cancer types, treatment settings, and total cisplatin cycles, and is common among four previous Japanese prospective studies examining short hydration methods[6]. In future large-scale randomized controlled trials, as the authors suggest, more patient-centric outcomes, such as cisplatin dose intensity, treatment completion rates, relapse-free survival, progression-free survival, and overall survival, would be more compelling, particularly when restricted to one cancer type and the same treatment intent. Fifth, while the introduction of this paper referred to the potential disadvantages of diuretics (e.g., administration time and vascular pain with mannitol; dehydration, electrolyte abnormalities, and possible nephrotoxicity; and ototoxicity with furosemide when combined with cisplatin) as the rationale for omitting them, this study did not present data demonstrating that the diuretic-free regimen successfully mitigated these issues. Given that the renal outcomes were not clearly superior to short hydration regimens that use diuretics, these other benefits are crucial in justifying the omission of diuretics.

We commend the authors for addressing an understudied question and agree that randomized trials comparing regimens with and without diuretics are warranted. Such trials should measure the potential benefits of omitting diuretics as prespecified endpoints and select primary endpoints that directly reflect patient benefit, ideally restricted to a single cancer type and uniform treatment intent. These considerations are critical in designing trials to establish an optimal hydration approach for cisplatin-based chemotherapy.

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https://doi.org/10.1272/jnms.JNMS.2026_93-305

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of Interest:** NB has received research grants from Pfizer Inc. and honoraria from Bristol Myers Squibb, Astellas, Taiho Pharmaceutical, and Eli Lilly. The other authors declare no conflicts of interest.

**Declaration of Generative AI and AI-Assisted Technologies in the Writing Process:** During the preparation of this work, the authors used a generative AI tool to assist with English language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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