Cisplatin-induced renal toxicity in elderly people

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Abstract: Despite available prevention and treatment measures, such as hydration, diuresis, magnesium supplementation, and amifostine, renal toxicity is still one of the major dose-limiting side effects of cisplatin. The aim of this review is to discuss the issue of cisplatin-induced nephrotoxicity in the elderly. Compared with young patients, the incidences of cisplatin-induced nephrotoxicity and acute kidney injury (AKI) in elderly patients are significantly increased, and survival time may be decreased. Following cisplatin treatment of elderly patients, tubulointerstitial injuries will be significantly aggravated based on their original age, both for acute injuries due to cell necrosis and exfoliation and chronic injuries due to interstitial fibrosis, tubular atrophy, and dilatation. The high incidence of cisplatin-induced nephrotoxicity in elderly patients may be associated with renal hypoperfusion; increased comorbidities, such as chronic kidney disease (CKD), cardiovascular disease, and diabetes mellitus; increased use of combined drugs [especially non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme *inhibitor* and angiotensin receptor blockers (ACEI/ARB), and antibiotics]; decreased clearance of cisplatin; and high plasma ultrafilterable cisplatin. Considering hemodynamic stability and water balance, short duration and low volume hydration may be more suitable for treating elderly people. With the increasing popularity of low-dose daily/weekly regimens, we do not recommend routine diuretic treatment for elderly patients. We recommend using a less nephrotoxic platinum if large doses of cisplatin (100mg/m^2) are needed.

Keywords: acute kidney injury, aging, cisplatin, renal toxicity, risk factors

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Introduction

Cisplatin was first synthesized in 1845 by Michele Peyrone and was known as Peyrone's chloride, but its anticancer activity was not discovered until 1969.[1] In a phase I clinical study of cisplatin, it was found that a dose of 40 mg/m^2 caused severe renal damage, accompanied by emesis and ototoxicity. Subsequent animal studies found that the renal damage caused by cisplatin might be preventable through aggressive hydration.[2] An increasing number of measures, such as hydration, OCT2 inhibitors (cimetidine or metformin), and high-dose glutathione,[3,4] have been reported to alleviate cisplatin-induced nephrotoxicity. However, even with the use of the above-mentioned measures, the incidence of cisplatin-induced renal toxicity remains high.

Although malignant tumors occur at all ages, cancer disproportionately affects individuals 65 years and older.[5,6] Among these individuals, patients ≥70 years of age account for 41% of the whole population with common tumor types.[7] In the United States (US), most patients diagnosed with cancer are ≥65 years old, and it has been predicted that the cancer incidence among elderly people will increase by 67% from 2010 to 2030.[8] Despite the increasing variety of available chemotherapeutic drugs, including the increasing availability of targeted drugs, cisplatin is still one of the most commonly used chemotherapeutic drugs in the clinic due to its broad anticancer effect, low price, and sufficient evidence-based efficacy. Currently, according to the National Institutes of Health, more than 273,000 cancer-related clinical

trials are being conducted worldwide, in which the majority of the tested drugs are cisplatin- and platinum-based agents.[9] Recent studies have found that cisplatin-induced acute kidney disease (AKI) occurs in as many as 31.5% of cases even after hydration treatment.[10] Both our previous single-center study and a meta-analysis showed that the incidence of cisplatin-induced AKI in elderly people was higher than that in younger patients.[11,12] Elderly patients will clearly benefit from cisplatin-based therapy, but renal toxicity limits its clinical use and can even lead to the discontinuation of chemotherapy. Clarifying the incidence of cisplatin-induced AKI in elderly patients and exploring the risk factors of elderly patients and their impact on long-term prognoses (all-cause mortality and end-stage renal disease) will help to reduce the occurrence of cisplatin-induced AKI and avoid unnecessary reductions or discontinuations of cisplatin. The review will focus on these topics.

Incidence of cisplatin-related renal toxicity in elderly patients

Dose-related renal toxicity is a dose-limiting side effect of cisplatin. Renal toxicity is one of the main causes of treatment discontinuations, accounting for 25–30% of all treatment discontinuations due to adverse events.[13] Compared with young patients, elderly patients usually have a lower renal reserve function, a decrease in the ability to repair injury and more comorbidities, which greatly increases their chances of developing drug-related AKI. Medications account for ~20% of AKI cases among older patients.[14] The incidence of cisplatin-induced renal toxicity greatly varies among elderly patients, as reported in different studies. Using information from our previous meta-analysis, updated in December 2019, we provide data from studies on cisplatin-induced renal toxicity in elderly patients in Table 1. The overall incidence of cisplatin-induced renal toxicity in elderly patients is 10.06% (121/1203), which is significantly higher than that in young patients (6.51%, 289/4439).[13,15–34] Most literature results show that the incidence of renal toxicity in elderly patients after cisplatin use is higher than that in young patients. Due to the intolerance of Asian individuals to high-dose cisplatin chemotherapy, some Asian researchers have adopted a low-dose, daily chemotherapy regimen for the treatment of non-small cell lung cancer (NSCLC). Because the total dose of cisplatin is similar, this treatment can significantly reduce the

incidence of renal toxicity and improve the completion rate of chemotherapy cycle.[20,35] Comparing the administration of 30–40 mg/m² cisplatin for 3 consecutive days (A1) with 80–120 mg/m² cisplatin for only 1 day (A2) to elderly patients (both A1 and A2 were given hydration), the results showed that the incidence of grade III/IV renal damage in A2 (15.4%) was significantly higher than that in A1 (2.5%).[29] The incidence of cisplatin-induced renal toxicity varies greatly among different types of tumors due to the different chemotherapy regimens, initial doses, and accumulated doses used. Our previous report found that the risk of renal toxicity in older patients was 5.81 times higher than that in nonelderly patients in those with oral squamous cell carcinoma.[12] Head and neck tumors were the first type of cisplatin-induced nephrotoxicity reported,[10] possibly due to the high initial and cumulative doses of cisplatin, concurrent radiotherapy, and increased risk of hypovolemia due to the inability to eat. In recent years, the standard dose of 100 mg/m² cisplatin administered triweekly has been changed to weekly administration of cisplatin 40 mg/m² in the chemotherapy regimen for head and neck tumors because of its high toxicity (especially nephrotoxicity) and the high incidence of treatment discontinuation.[36] Most of the cisplatin-related renal complications reported in the literature are defined as renal toxicity, but there are a few reports of cisplatin-induced AKI. We retrieved all the studies on cisplatin-induced AKI and aging reported in PubMed before December 2019; seven articles were found (Table 2).[10,11,37–41] AKI in three of the included studies was defined as an increase from baseline creatinine of >25%.[10,11,37] The overall incidence of cisplatin-induced AKI in elderly patients was 24.49% (9.46–48.57%), which is significantly higher than that in young patients (15.39%). The incidence of cisplatin-induced AKI in elderly patients was significantly higher than that of cisplatin-induced renal toxicity partly because three of the included studies defined AKI as a 25% increase in baseline creatinine, one as 20% reduction in Ccr, and two as a 0.3–0.4 mg/dl increase in baseline creatinine, which is more sensitive than the commonly used definition of renal toxicity. Our previous study reported that the incidence of cisplatin-induced AKI in elderly patients was 9.46%,[11] which was relatively lower than that of the other three studies. This may be because the recording time of AKI in our cohort was within 30 days after the first cycle of cisplatin, and our initial dose and cumulative dose were

Table 1. General data from cisplatin-induced renal toxicity studies.

Study	Nationality	Tumor types	Total elderly patients	Total renal toxicity (%)	Renal toxicity grade 1/2	Renal toxicity grade 3/4 or 3–5	Total young patients	Total renal toxicity [%]	Initial dose mg/m²	Other chemotherapy drugs	Hydration
Alberts et al.[15]	America	Ovarian cancer	58	1 (1.72%)	NA	1	85	1 (1.18%)	100	Cyclophosphamide	Yes
Barutca et al.[34]	Turkey	Mixture	13	4 (30.77%)	4	0	22	4 (18.18%)	NA#	Mixture	Yes
Kothari et al.[17]	America	Ovarian cancer	23	0	NA	0	86	5 (5.81%)	100 (IP)	Paclitaxel (IP=109, IV=96) or docetaxel (IV=13)	No
Kunos et al.[18]	America	Cervical cancer	103	2 (1.94%)	NA	2	232	15 (6.47%)	40	Fluorouracil or hydroxyurea	No
Langer et al.[19]	America	NSCLC	88	47 (53.41%)	44	3	500	198 (39.6%)	75	Etoposide or paclitaxel	No
Früh et al.[16]	Canada	NSCLC	157	1 (0.64%)	NA	1	1757	12 (0.68%)	Mixture	NA	No
Siu et al.[21]	Canada	Small-cell lung cancer	88	0	NA	0	520	3 (0.58%)	25 for 3 consecutive days	Mixture	Yes
Cheng et al.[23]	China	NSCLC	17	0	NA	0	34	0	25 for 3 consecutive days	Vinorelbine	No
Gao et al.[24]	China	NSCLC	30	1 (3.33%)	1	0	32	1 (3.12%)	40 for 2 consecutive days	Gemcitabine	Yes
Ge et al.[25]	China	NSCLC	36	1 (2.78%)	1	0	34	1 (2.94%)	25	Gemcitabine	No
Liu et al.[26]	China	NSCLC	22	3 (13.64%)	3	0	23	3 (13.04%)	25 for 3 consecutive days	Gemcitabine	Yes
Lv and Ni[27]	China	Mixture	66	32 (48.48%)	32	0	56	0	40mg for 3 consecutive days or 20mg for 5 consecutive days	Mixture	Yes
Peng[33]	China	NSCLC	46	0	0	0	30	0	35	Gemcitabine	Yes
Sun et al.[28]	China	NSCLC	33	2 (6.06%)	2	0	30	1 (3.33%)	30 for 3 consecutive days	Vinorelbine	Yes
Tan[29]	China	NSCLC	66	4 (6.06%)	NA	4	56	1 (1.79%)	30–40 for 3 consecutive days or 80–120	Mixture	Yes
Wu et al.[30]	China	NSCLC	100	4 (4%)	2	2	100	0	15 for 3 consecutive days (elderly) or 15 for 5 consecutive days (non-elderly)	Gemcitabine (elderly) or vinorelbine (non-elderly)	No
Ye et al.[31]	China	Oral squamous-cell carcinoma	72	8 (11.11%)	NA	8	72	1 (1.39%)	80/60	Pingyangmycinum and vincristine	Yes
Zhang et al.[32]	China	NSCLC	48	4 (8.33%)	NA	4	152	8 (5.26%)	NA*	Mixture	No
Gridelli et al.[13]	Italy	NSCLC	92	7 (7.61%)	7	0	447	26 (5.82%)	75	Pemetrexed	No
Ohe et al.[20]	Japan	NSCLC	12	0	0	0	26	0	25	Docetaxel	Yes
Takeuchi et al.[22]	Japan	Esophageal cancer	33	0	NA	0	145	9 (6.21%)	40	Fluorouracil	No

IP, intraperitoneal; IV, intravenous; NA, not available; NSCLC, non-small-cell lung cancer.
#80–100 mg/m2 per cycle; *70–100 mg/m² per cycle.

Table 2. General data from cisplatin-induced AKI studies.

Study	Tumor types	Aging	AKI defined	Total elderly n	AKI n (%)	Total young patients	AKI n (%)	Initial dose [mg/m²]	Accumulated dose	Hydration
Cubillo et al.[38]	Multiple	≥70	increased Scr≥0.4mg/dl	49	21 (42.86%)	NA	NA	27/week	245 mg/m²	Yes
Kimura et al.[41]	head and neck cancer	≥65	20% reduction in Ccr	54	15 (27.78%)	52	12 (23.08%)	80	160 mg/m² (two courses)	Yes
Latcha et al.[10]	Multiple	≥66	Increase baseline creatinine>25%	123	55 (44.72%)	698	190 [27.22%]	No mention	41.9% was >250 mg/m²	Yes
Liu et al.[11]	Multiple	≥60	Increase baseline creatinine>25% or KDIGO criteria	349	33 (9.46%)	178	6 (3.37%)	64.32	112.42 mg [for the first cycle]#	Mostly (93.7%)*
Motwani et al.[39]	Multiple	>70	Increase baseline creatinine≥0.3 mg/dl	278	77 (27.7%)	1840	211 (11.47%)	NA	25% was >150mg [for the first cycle]	NA
Thyss et al.[37]	Multiple	≥80	Increase baseline creatinine>25%	35	17 (48.57%)	NA	NA	62.5	300.57 mg	Yes
Yamamoto et al.[40]	Gynecological cancer	≥65	RIFLE criteria	28	10 (35.71%)	84	20 (23.81%)	61.72	233.19 mg/m²	Yes

AKI, acute kidney injury; Ccr creatinine clearance; N, number; NA, not available; Scr, serum creatinine.
#61.6% elderly patients have only one cycle of cisplatin.
*93.7% patients were given hydration.

relatively low (64.32 mg/m² and 112.42 mg, respectively).[11] Yamashita *et al.* and Wen *et al.* reported that the incidence of cisplatin-related AKI was 6.76% and 14.29% in patients older than 50 years old, respectively.[42,43] The incidence of cisplatin-induced AKI tends to increase with increasing of age (50 years, 11.5%; 60 years, 9.46%; 65 years, 37.04%; 70 years, 29.97%; 80 years, 48.57%). The incidences of cisplatin-induced AKI in elderly patients were both more than 40% in studies by Thyss in 1994 and Cubillo in 2001.[37,38] The changes of serum creatinine (Scr) in the latter two studies were the difference between the baseline Scr level before treatment and the maximum Scr level at the completion of all courses of cisplatin, and the patients in the two groups were older (aged ≥80 and ≥70, respectively).[37,38] Cubillo found that, after the first chemotherapy course, the maximum Scr level was only reached in 30% of patients, after the second and third courses in 34%, and after the fourth course or later in 14%.[38] Only 30% of patients had the highest level of creatinine in the first cycle. In Cubillo's study, ifosfamide and mitomycin were used in 10 patients, which may have further increased the incidence of AKI.[38] Because of the high incidence of cisplatin-induced AKI in elderly patients, we recommend that Scr levels be measured at least twice during each chemotherapy cycle (before and after cisplatin treatment). In elderly patients whose Scr levels tend to increase before and after treatment (rather than simply evaluating the absolute value of Scr), the number of Scr tests should be increased. Although the incidence of cisplatin-induced AKI in elderly patients is high, severe renal insufficiency rarely occurs. Five studies (including a total of 584 elderly patients) did not report that patients needed dialysis.[10,11,38] Only 0.49% (2/419) of elderly patients were AKI grade 3 (KDIGO stage 3, RIFLE-Failure or above).[11,37,40] As the evidence of some opinions in this part comes from only one or two studies or small sample size studies, more large sample studies are needed in the future.

Long-term renal outcome and survival of elderly patients with cisplatin-induced renal toxicity

In the study of cancer patients, it is suggested that, with the progress in AKI classification, the mortality rate of patients may be increasing.[44,45] In a cohort study of head and neck tumors treated with cisplatin ($n=233$), patients with stage III AKI

(KDIGO) had a lower survival rate than patients who did not develop AKI or developed stage I or II AKI. With the progress of the AKI classification, the risk of death is increasing (hazard ratio of grade I, II, and III are 1.54, 1.76, and 3.49, respectively).[46] Another Japanese study found that the median overall survival times of severe (KDIGO, ≥stage 2) cisplatin-induced AKI (CIA) patients were significantly lower than those of non-CIA patients.[47] However, compared with moderate CIA patients (KDIGO, stage 1), non-CIA patients had no survival advantage within 50 months.[46,47] On the other hand, even patients with mild CIA have lower long-term survival (more than 5 years) than non-CIA patients. For tumors that have a higher 5-year survival rate, CIA may have a more significant negative effect on survival. CIA patients have a short survival time, but it is unknown whether this is due to a dose reduction, alternative agents with inferior oncologic effects or treatment interruption. When AKI occurs at the end of the first-course chemotherapy, 14.7% of patients underdo a dose reduction, 13.2% of patients convert to other non-cisplatin regimens, and 14.7% of patients stop chemotherapy during the subsequent chemotherapy course.[48] The worse 3-year overall survival of CIA patients may be related to the above-mentioned factors.[48] Additional proof comes from the fact that the causes of death of CIA patients are related predominantly to recurrent cancer (44%) or the development of a secondary malignancy elsewhere (40%), but not due to cardiovascular events.[46]
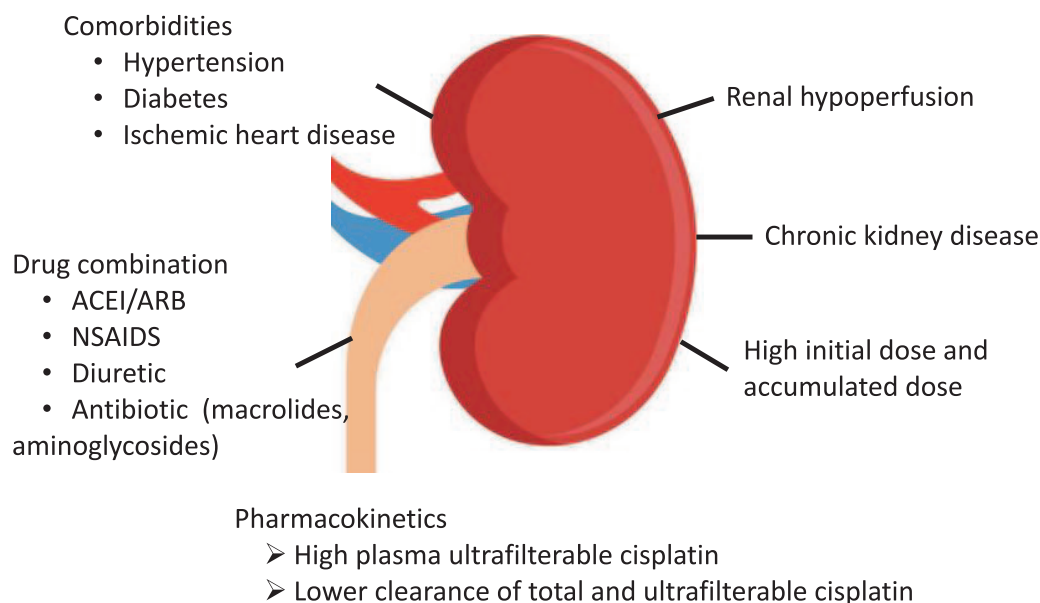
In addition to increasing the risk of death, cisplatin-induced AKI may result in irreversible renal injury.[49] Latcha conducted a retrospective study of 859 adult patients who had survived for longer than 5 years after receiving cisplatin treatment.[10] Within 1 month of the completion of cisplatin treatment, patients with CKD stage 3 or above increased from 11% to 31%.[10] The impact of cisplatin on renal function tends to rapidly decline over a short period of time (1 month) and then partially recover, but most of the renal function of most patients does not recover to the baseline level before treatment. The long-term impact of cisplatin on renal function cannot be ignored. The severity of cisplatin-induced AKI may have an adverse effect on long-term renal function. Patients with KDIGO stage 3 AKI had the greatest decrease in *estimated glomerular filtration rate (*eGFR) (38%) from baseline to 12 months and had the lowest eGFR at 12 months (from 120 to 75 ml/min/1.73 m^2).[46] The percentage of patients with eGFR<60 ml/min (CKD 3 and above) was 31% in KDIGO stage 1 and 2 AKI. However, the percentage of patients was much higher in KDIGO stage 3 AKI (54%).[46] Therefore, for elderly patients treated with cisplatin, it may be necessary to re-evaluate their renal function 1 month after treatment, especially in patients with severe AKI.

Renal pathology changes in elderly patients with cisplatin-induced renal toxicity

The main pathological change of cisplatin-induced renal injury is tubulointerstitial injuries, of which necrosis and the sloughing of proximal tubular epithelial cells are the most obvious. These findings have been confirmed in both rat and human autopsy studies.[50,51] Scattered vacuolar degeneration and sloughing could also be observed in distal tubular epithelial cells, but to a lesser degree than in the proximal tubules. In the human renal autopsy study, diffuse dilation of the proximal and distal tubules with intraluminal granular or hyaline casts could be observed in 70% of patients. The morphology epithelial cells of the collecting ducts can also be used as a sign of early damage, such as pyknosis and shrunken nuclei, swelling and desquamation of some ducts and so on.[50] Chronic cisplatin treatment may result in irreversible renal damage, such as cyst formation, interstitial fibrosis (both confirmed in human and animal studies), and even glomerulosclerosis (only in animal model).[51,52] Focal interstitial fibrosis, tubular atrophy, and dilatation were observed in human kidneys 5 months after the last course of cisplatin.[53] The number of renal tubular cells decreased in aging rats in the blank control group and renal tubular atrophy, steatosis, and other aging kidney changes were also found.[54] Tubular length and volume can also be reduced markedly, and sparse areas of scarring, tubular atrophy, and tubular diverticula are common in the kidneys of elderly individuals. In addition, an increased interstitial volume, infiltration of mononuclear cells, and diffuse areas of fibrosis are all hallmarks of the aging kidney.[55] After treatment of elderly patients with cisplatin tubulointerstitial injuries, such as acute injuries of both cell necrosis and sloughing, and chronic injuries of interstitial fibrosis, tubular atrophy and dilatation were significantly aggravated based on age. Our previous study in aged rats confirmed that, after 72 h of cisplatin treatment, proximal tubular dilatation, proteinuria casts, loss of the tubule brush border, and disarrangement of cells could be seen in certain tubules.[54]

Comorbidities
- Hypertension
- Diabetes
- Ischemic heart disease

Renal hypoperfusion

Chronic kidney disease

Drug combination
- ACEI/ARB
- NSAIDS
- Diuretic
- Antibiotic (macrolides, aminoglycosides)

High initial dose and accumulated dose

Pharmacokinetics
➢ High plasma ultrafilterable cisplatin
➢ Lower clearance of total and ultrafilterable cisplatin

Figure 1. Risk factors for, and the pharmacokinetics of cisplatin-induced renal toxicity in, elderly patients. Renal hypoperfusion, a high incidence of CKD, high initial and cumulative doses, multiple comorbidities (such as hypertension, diabetes, and ischemic heart disease), and drug types (ACEI/ARB, NSAIDS, diuretic, and antibiotic) are risk factors for cisplatin-induced renal toxicity in elderly patients. Compared with young patients, elderly patients have high plasma levels of ultrafilterable cisplatin, and a lower clearance of total and ultrafilterable cisplatin at a dose of 50 mg/m² or more.
ACEI/ARB, angiotensin-converting enzyme *inhibitor* and angiotensin receptor blocker; CKD, chronic kidney disease; NSAIDS, non-steroidal anti-inflammatory drugs.

Glomerular injuries are less common than tubulointerstitial injuries because they only occur with high exposure.[52] Therefore, in some studies of human kidney tissues, no evidence of cisplatin-induced glomerular damage was found (light or electron microscopy).[53,56] However, cisplatin may directly damage glomerular cells and cause proteinuria even in the nephrotic range.[52] The ultrastructural alterations induced by 2.5–4 mg/kg cisplatin were studied by transmission electron microscopy in guinea pigs. The results revealed foci of damage in all glomerular components, such as luminal deformities and constriction of the glomerular capillaries, focal thickening and lamination of the glomerular capillary basement membrane, focal foot process fusion of podocytes, and so on.[57] The main glomerular changes that occur with aging are decreased numbers of glomeruli, glomerulosclerosis, glomerular hypertrophy, and podocytopenia.[55] We speculate that chronic cisplatin treatment may aggravate aging-related glomerulosclerosis in elderly patients. However, evidence from animal model studies, even renal pathological results of elderly patients treated with cisplatin, are needed.

Vascular injuries caused by cisplatin may be due to an atypical hemolytic uremic syndrome.[58] Renal vascular pathology shows concentric subintimal thickening of small arteries and arterioles, with loose mucoid-appearing material and fibrin thrombi in afferent arterioles and glomerular capillaries.[58] From the age of 18 years to 80 years, renal plasma flow and effective renal plasma flow decline steadily.[55] Microangiopathy and aging may both cause reduced renal blood flow, which may lead to decreased GFR and hypoxic tubular damage in elderly patients.[59]

Risk factors for cisplatin-induced renal toxicity in elderly patients

Renal hypoperfusion
Renal hypoperfusion is the most common classification and the first injury factor of AKI reported in China (Figure 1).[60] Renal hypoperfusion accounts for 77.7% of all AKI causes in elderly patients.[60] Nausea, vomiting, diarrhea, and poor appetite in elderly patients after cisplatin treatment can lead to renal hypoperfusion. The incidences of nausea,

vomiting, and diarrhea in elderly patients after cisplatin treatment are 89.77%, 68.18%, and 37.5%, respectively.[19] Although antiemetic and antidiarrheal drugs can be used clinically to prevent the occurrence of vomiting and diarrhea, it is difficult to improve the poor appetite of patients, who are often in a negative capacity balance. The incidences of cardiovascular and cerebrovascular diseases in elderly patients were significantly higher than those in young patients.[11,12] Considering the increased risk of heart failure or edema in elderly patients, fluid replacement or hydration therapy may be more cautious than in young people. Moreover, the use of mannitol or furosemide diuretics may speed up the excretion of cisplatin, whereas there is a risk of dehydration due to excessive diuresis. A recent systematic review of strategies to prevent cisplatin-induced nephrotoxicity found that mannitol may be beneficial only in patients receiving high-dose cisplatin (e.g. 100 mg/m^2).[61] When the dosage of cisplatin is low, the risk of excessive diuresis may be greater than the benefit of increasing cisplatin excretion. In addition to the risk of excessive diuresis, high-dose mannitol may also cause osmotic nephropathy due to high plasma osmotic pressure.[62] It is suggested that the plasma osmotic pressure should be monitored closely before and after mannitol treatment so that the plasma osmotic pressure after treatment is less than 350 mOsm/(kg.H$_2$O) or the plasma osmotic pressure difference before and after treatment is less than 55 mOsm/(kg.H$_2$O). Angiotensin-converting enzyme *inhibitor* and angiotensin receptor blocker (ACEI/ARB) medication is more frequently used in older patients than in younger patients.[11] ACEI/ARBs can cause vasodilation of both afferent and efferent arterioles, but the effect is more significant in the latter.[63] The resulting aggravated renal ischemia constitutes a higher risk for AKI. Univariate and multivariate logistic regression analyses have revealed that the use of ACEI/ARB is an independent risk factor for developing cisplatin-induced AKI in elderly patients.[11] Therefore, discontinuation of ACEI/ARB suggested when patients undergo chemotherapy with cisplatin. Early diagnosis of an insufficient blood volume and appropriate treatment are important strategies to reduce cisplatin-induced renal toxicity. In addition to central venous pressure (CVP) and other invasive indicators, there are noninvasive indicators for the rapid determination of blood volume insufficiency, such as an orthostatic position, heart rate increase >30 beats/min, systolic pressure decrease >20 mmHg, diastolic pressure decrease >10 mmHg, axillary dryness, oral mucosa dryness,

and a longitudinal groove pattern on the surface of the tongue.[64] Other factors, such as an increase of renal atherosclerosis in elderly patients,[65] can also weaken the compensatory ability of unilateral or bilateral renal arteries, leading to a significant decrease in renal perfusion in elderly patients with an insufficient blood volume.

Chronic kidney disease

GFR steadily decreased with normal aging, beginning at about 30 years of age.[66] The average yearly decline of GFR between 30 and 75 years of age in healthy individuals is approximately 0.7–0.9 ml/min.[67] Half of adults over age 70 can have GFR<60 ml/min/1.73 m^2.[68] It is generally believed that the risk of cisplatin-induced nephrotoxicity is higher and more serious in elderly patients with renal insufficiency. However, our meta-analysis showed that the risk of nephrotoxicity was higher in elderly patients with normal renal function. The results were consistent with Latcha's research.[10] After cisplatin treatment, 64% of patients with CKD stage 1 progressed to CKD stage 2 or above. By contrast, the percentages of patients who progressed to CKD 2 and CKD 3 were 33% and 6%, respectively,[10] possibly because a lower cumulative dose of cisplatin tends to decrease in patients with renal insufficiency.[10] In patients older than 80 years, the incidence of AKI is 85.71% in those with creatinine clearance (CC, using the Cockroft and Gault formula) greater than 60 ml/min, and 39.29% in those with CC less than 60 ml/min.[37] Similarly, we also found that the total dose of cisplatin in the CC ⩾60 group was 115 mg/m^2 (total dose/course), which was significantly higher than that in the CC <60 group. None of the patients in the above-mentioned studies progressed to CKD 5 or required dialysis treatment.[10,37] For elderly patients with CKD 3 or above, cisplatin therapy may be safe, but the initial and cumulative doses of cisplatin need to be reduced and the ratio of serum creatinine and eGFR changes should be closely monitored rather than the absolute value.

Initial dose and accumulated dose

A high initial dose of cisplatin (⩾50 mg/m^2) may increase the incidence of cisplatin-induced renal toxicity, even when adequate hydration therapy is used. A summary of studies that used an initial dose of cisplatin greater than 50 mg/m^2 in presented in Table 1.[1,13,15,19,29,31] and the results show that the incidence of cisplatin-induced renal toxicity is 19.94% in elderly patients and 19.57% in

young patients, which are both significantly higher than the total incidences of cisplatin-induced renal toxicity reported in Table 1 (10.06% and 6.51%, respectively). In Langer's study, the initial dose of cisplatin was 75 mg/m². There was no clear indication that hydration therapy was provided. The incidence of renal toxicity was 53.41% in elderly patients and 39.6% in young patients.[19] High-dose cisplatin treatment may significantly increase the incidence of renal toxicity and reduce the completion rate of treatment, even leading to treatment discontinuation. Therefore, in the treatment of NSCLC or head and neck cancer, increasing evidence suggests a low-dose, daily, or weekly chemotherapy regimen. This regimen has the same efficacy and less nephrotoxicity than a one-time high dose regimen.[20,35,36,69] In Ohe's study, elderly (≥75 years) patients with NSCLC were given chemotherapy consisting of 25 mg/m² cisplatin on days 1, 8, and 15. A small dose of hydration therapy was given (1500 ml of normal saline).[20,70] In the phase I study, none of the 12 elderly patients had renal toxicity.[20] In the phase II study, only 1 of 33 patients (3.03%) was observed to have grade 2 renal toxicity.[70] Feliu *et al.* also showed that of a total of 190 GEM-CDDP courses (treatment consisted of 50 mg/m² cisplatin on day 1 plus 1000 mg/m² gemcitabine on days 1 and 8), only two elderly (≥70 years) patients (4.35%) had grade 1/2 nephrotoxicity.[71]

In addition to a high initial dose, a higher cumulative dose may be linked to increase the risk of renal toxicity.[72] Among the seven studies listed in Table 2 on cisplatin-induced AKI, the incidence of AKI in elderly patients reported in our study (defined as an increase in Scr levels ≥25% from the baseline with 30 days after the first cycle of cisplatin) was only 9.46%, and the cumulative dose (for the first cycle) of our elderly patients was relatively lower (112 mg).[11] Latcha reported the incidence of cisplatin-induced AKI in elderly patients was 44.72%.[10] The recording time of AKI was also within 30 days after the first cycle of cisplatin, but cumulative dose was relatively higher (the initial dose was not given), 41.9% of patients were higher than 250 mg/m², 15.7% were more than 400 mg/m².[10] They also found that the lowest cumulative dose of cisplatin (≤100 and 101–250 mg/m²) were associated with increases in eGFR compared with the highest cumulative dose category (>700 mg/m²).[10] There was no significant difference in the risk of AKI between patients with cumulative dose greater than 250 mg/m² and

patients with cumulative dose greater than 700 mg/m².[10] According to the analysis of Thyss,[37] the incidence of AKI was 25% in patients with cumulative dose ≤100 mg, and about 50% in patients with cumulative dose 101–250, 251–400, and 551–700 (50%, 56.25%, and 50%). In Ohe's study, the initial dose (25 mg/m²) and cumulative dose/course (75 mg/m²) were very low, and no renal toxicity occurred in elderly patients over 75 years old.[20] Therefore, the cumulative dose >250 mg/m² may be related to increase the risk of acute renal injury in the elderly.

Role of comorbidities and drug combination

Comorbidities, including hypertension, diabetes mellitus, and cardio-cerebrovascular disease, are more common in elderly patients than in younger patients.[11,12] A history of diabetes mellitus and a history of cardiovascular disease may be risk factors for severe cisplatin-induced AKI in clinical research. The odds ratios of patients with history of diabetes mellitus and cardiovascular disease are even higher than those of the cisplatin dosage (mg/m²) or stage 4 cancer.[47] Our results confirm that the risk of platinum-related nephrotoxicity is significantly increased in the high comorbidity rate group.[12] However, the kidneys of diabetic rats are protected against cisplatin nephrotoxicity, possibly due to the early renal hyperfiltration in diabetes mellitus and deficiencies of the active transport of the drug in tubular epithelial cells, which could decrease the accumulation of cisplatin in plasma and kidneys.[73–75] The histopathology of renal tissue does not induce renal injury in streptozotocin-induced diabetic mice.[75] However, cohort studies of elderly patients with lung cancer found that hypertension, diabetes, and ischemic heart disease may be linked to reducing renal resistance to cisplatin-induced nephrotoxicity.[76] Hypertension, diabetes mellitus, and ischemic heart disease could significantly increase the incidence of cisplatin-induced renal toxicity in elderly patients with lung cancer, which could significantly increase the incidence rate from 14% to 75%.[76] An important reason for the inconsistency between the animal experiments and clinical cohort studies is that the elderly patients in the cohort studies have a long history of hypertension and diabetes mellitus that may be long enough to produce pathological changes in the kidneys and accelerate the aging of the kidneys. In addition to the physiological age, nephrosclerosis and intrarenal arterial sclerosis are accelerated by long-term hypertension and diabetes mellitus.[77,78] Nephrosclerosis and intrarenal

arterial sclerosis are associated with chronic ischemic tubulointerstitial damage,[78] the major target of cisplatin-induced nephrotoxicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly known to cause AKI through multiple mechanisms, and account for 16% of all drug-related renal failure.[79] Because of cancer pain, elderly patients often use NSAIDs before and after cisplatin treatment. The incidence of cisplatin-induced AKI may be significantly increased in elderly patients with NSAIDs. AKI occurred in all 12 elderly patients who used NSAIDs in our previous cohort.[11] Research on thoracic malignancies also suggested that cardiac disease and the use of NSAIDs were associated with cisplatin-induced AKI. NSAIDs should be avoided as much as possible during cisplatin treatment. In addition to ACEI/ARB, diuretics and NSAIDs, elderly patients should be alerted to the potential of the combined use of antibiotics (such as aminoglycosides and macrolides), uric acid-lowering drugs (allopurinol and colchicine) and antiarrhythmic drugs (quinidine, procainamide) to lead to drug-induced AKI during cisplatin treatment. A recent study showed that increasing the duration of antimicrobial prophylaxis is associated with increased odds of developing AKI.[80] The adjusted odds ratio of AKI is approximately 1.8 after prolonged use for more than 3 days.[80] Histopathological findings of the kidney obtained by autopsy confirm that patients who received antibiotics following cisplatin therapy show much more necrosis and desquamation of epithelial cells of the proximal tubules than those who received cisplatin alone.[50]

Pharmacokinetics

Compared with nonelderly patients, elderly patients (older than 70 years) have slow ultrafilterable cisplatin plasma clearance and persistently high plasma levels of ultrafilterable cisplatin at 48 h after receiving an initial dose of 50–65 mg/m².[81] A dose of 80 mg/m² cisplatin was administered to patients with lung cancer, and the results showed that increasing age was a significant predictor of lower clearance of total and ultrafilterable cisplatin.[82] The authors speculated that the decrease of the cisplatin clearance rate in elderly patients may be related to the decrease of renal function and plasma albumin.[82] Even after hydration, diuresis and other measures, in elderly patients, the glomerular filtration rate, renal blood flow and cisplatin clearance rate decrease compared with those of young patients. When the initial dosage of cisplatin is more than 50 mg/m², the

decrease of a cisplatin clearance rate, the increase of the cisplatin maximum plasma concentration,[83] the increase of the ultrafilterable cisplatin concentration caused by anemia, and the decrease of plasma albumin,[82] may be all pharmacokinetic bases for the increase of renal toxicity in elderly patients. However, in another study of lung cancer with normal renal function (with a mean creatinine clearance of 93.3 ml/min in elderly patients), different conclusions were drawn. At a dose of 25 mg/m² cisplatin, the pharmacokinetics (clearance, volume of the distribution, and the area under the concentration-time curve) of cisplatin were not different between elderly and nonelderly patients.[84] The pharmacokinetics indicators (especially clearance) of cisplatin at low doses and in elderly patients with relatively normal renal function remained normal. This study further may support the use of low-dose fractional administration of cisplatin in elderly patients from the pharmacokinetic point of view. In addition to the effect of the initial dose, a reduced ability to clear ultrafilterable cisplatin with repeated courses has already been reported.[85] In a 70-year-old ovarian cancer patient with normal renal function, the plasma clearance of cisplatin at the second course was only 33% of that at the first course.[86] With an increase of the initial dose (≥50 mg/m²) and treatment course, elderly patients may have reduced cisplatin clearance and increased kidney exposure, which could increase the risk of cisplatin-induced nephrotoxicity.

Clinical strategies to prevent cisplatin-induced renal toxicity

Hydration is the first and the most reasonable strategy to decrease the incidence of cisplatin-induced renal toxicity (see Table 3). Animal studies have shown that hydration combined with mannitol diuretic therapy can alleviate cisplatin-induced nephrotoxicity before cisplatin is marketed.[2] It is estimated that 20–30% of elderly people may suffer from dehydration.[87] Appropriate hydration treatment is not only conducive to reducing the urinary cisplatin concentration and decreasing the proximal tubule transit time but is also conducive to maintaining the water balance and reducing the incidence of renal hypoperfusion in elderly people. Hydration should start before cisplatin treatment and be maintained for at least 3 days after treatment.[88] Compared with the total 6–12 l fluid volume of conventional hydration, short duration (over 2–6 h) and low volume hydration (2–4 l normal saline) may have the same effect

Table 3. Summary of the prevention and treatment strategies for cisplatin-induced renal toxicity in elderly patients.

Suggestions	Accessibility	Prevention and treatment strategies
Recommend	Usable	Short duration (over 2–6 h) and low volume hydration (2–4 l normal saline)
Recommend	Usable	Magnesium supplementation
Recommend	Usable	Amifostine
Recommend	Usable	Low-dose daily or weekly regimen
Not recommend	Usable	Diuretic (mannitol or furosemide)
Not recommend	Usable	The dose of cisplatin $\geqslant 100\,mg/m^2$
Not recommend	Unusable	Used ACEI/ARBs
Not recommend	Unusable	NSAIDS
Not recommend	Unusable	Antibiotic (macrolides, aminoglycosides)
Not recommend	Unusable	Contrast agent

ACEI/ARBs, ANGIOTENSIN-converting enzyme *inhibitor* and angiotensin receptor blockers, NSAIDS, nonsteroidal anti-inflammatory drugs.

in preventing cisplatin-induced renal toxicity.[61] Considering hemodynamic stability and volume balance, short duration, and low volume hydration may be more suitable for elderly people with hypertension and heart disease.

Mannitol is currently the most commonly used diuretic in the treatment of cisplatin-induced renal toxicity. In high-dose cisplatin treatment (100 mg/m²), mannitol may have taken a nephroprotective effect by reducing the concentration of cisplatin in the human kidney.[61,89] However, when the initial dosage of cisplatin is less than 100 mg/m², the addition of mannitol does not appear to be nephroprotective compared with hydration alone in a randomized trial.[90] In our previous meta-analysis, we did not find a positive result of diuresis therapy based on hydration treatment of elderly patients.[12] Some human studies have shown that furosemide may have a better nephroprotective effect than mannitol,[9,91] but there is insufficient evidence that furosemide is more nephroprotective than hydration alone. It should be noted that the excessive diuresis caused by mannitol or furosemide may lead to dehydration and inadequate renal perfusion, thus further deteriorating renal function in elderly people.

Magnesium supplementation may have a beneficial effect on decreasing Scr and increasing creatinine clearance or the estimated glomerular filtration rate in most studies.[92,93] Magnesium supplementation may be particularly important in elderly patients. A national survey in the US showed that 80% of older men (>70 years old) and 70% of older women did not meet the estimated average requirement for magnesium from food consumption.[94] We suggest that magnesium supplementation should be given to elderly patients treated with cisplatin.

Amifostine was the first FDA-approved cytoprotective and chemoprotective agent for the treatment of cancer in 1997 and is used to prevent cisplatin nephrotoxicity.[95,96] The dose-limiting toxicities of amifostine include emetic symptoms (nausea and vomiting) and transient hypotension. The incidence of systolic hypotension (a decrease in systolic blood pressure >20 mmHg) in elderly patients in each treatment cycle is range from 21% to 27%.[34,97] Additionally, 69.2% of elderly patients experienced at least one symptomatic hypotensive episode.[34] Compared with the nonelderly patients, interrupted infusion of amifostine is more often seen in elderly patients (≥70 years), and some of them cannot restart amifostine.[97] Hypotension does not result in medical sequelae in any patients,[97] and return to baseline within 30 min,[34] but we should still pay attention to the occurrence of cardiovascular and cerebrovascular events related to hypotension,

especially in elderly patients who have suffered from a prior myocardial infarction or cerebral infarction. Acetylcysteine (NAC) is a drug used in clinical practices as protector of contrast-induced nephropathy. The protective antioxidant activity of NAC against toxicity due to cisplatin has been reported in cells, animal models, and case reports.[98–101] However, there is still a lack of large-scale clinical research as evidence. Visacri conducted the first randomized, double-blind, placebo-controlled trial, and the results confirmed that low-dose oral NAC does not protect patients with head and neck cancer from cisplatin-related nephrotoxicity and oxidative stress.[102]

Conclusion

Cisplatin, as a classical chemotherapeutic drug that has been on the market for 40 years, is still the first-line treatment for many tumors because of its low price and sufficient amount of evidence-based medicine. Despite the prevention and treatment measures, such as hydration, diuresis, magnesium supplementation, and amifostine, renal toxicity is still one of the major dose-limiting side effects of cisplatin. Compared with young patients, the incidences of cisplatin-induced nephrotoxicity and AKI in elderly patients are significantly increased, and survival time may be decreased. With the increase of the initial dose and treatment course of cisplatin, aging may lead to the decrease of cisplatin clearance rate and increase of concentration of serum ultrafilterable cisplatin, which may aggravate tubulointerstitial injury based on age. To make matters worse, renal hypoperfusion; physiological renal function; a high incidence of CKD; increased comorbidities, such as cardiovascular disease and diabetes mellitus; and increased use of combined drugs (especially NSAIDs, ACEI/ARB, and antibiotics) may further increase the incidence of cisplatin-induced nephrotoxicity and AKI in elderly patients. We recommend that cisplatin is provided in a low-dose fractional administration to elderly patients with multiple risk factors for AKI. In terms of prevention and treatment strategies, we recommend short duration and low volume hydration, magnesium supplementation and amifostine for elderly patients treated with cisplatin. We do not recommend diuretic treatment for elderly patients. If a high dose of cisplatin ($100\,mg/m^2$) is needed, we recommend using a less nephrotoxic platinum formulation, such as carboplatin and oxaliplatin.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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