Title

Incidence of and risk factors associated with nedaplatin-related hypersensitivity reactions

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ABSTRACT

Background

Nedaplatin (NDP)-related hypersensitivity reactions (HSRs) trigger adverse clinical events. Prediction and prevention of NDP-HSRs are thus essential in order to minimize the risk and maximize the benefit of NDP therapy. However, the incidence of NDP-HSRs and the associated risk factors remain unclear.

Methods

We retrospectively examined patients who received NDP monotherapy between April 2011 and July 2015 in in Nagoya University Hospital. HSRs severity was defined according to Common Terminology Criteria for Adverse Events version 4 (CTCAE ver.4). Risk factors for NDP-HSRs were determined using multivariate logistic regression.

Results

Of 111 patients that received NDP monotherapy, 90 (81%) were female, and the median age was 59 years (range, 29–78 years). Eighty-eight patients had gynecologic cancer and 20 suffered from head and neck cancer.

Eight of 111 patients (7.2%) experienced NDP-HSRs, six of which developed in the second NDP cycle. However, all patients with NDP-HSRs were treated with carboplatin (CBDCA) for >3 cycles. Grade 3 and 4 HSRs developed in two patients. NDP-HSRs were significantly associated with a history of CBDCA-HSRs (odds ratio = 37.5, 95% confidence interval = 5.38–262, $p < 0.001$), and with the interval between NDP administration and the previous platinum treatment (odds ratio = 13.9, 95% confidence interval = 1.23–158, $p = 0.034$).

Conclusion

NDP-HSRs risk increases in patients with a history of CBDCA-HSRs, and in those administered NDP longer than 6 months after previous platinum treatment. Such individuals must be closely monitored if given NDP, even if they are expected to benefit from treatment.

Keywords

Nedaplatin, Hypersensitivity reactions, risk factors, cross-reactivity

Introduction

Hypersensitivity reactions (HSRs) are acute adverse events in chemotherapy; this has prompted significant research efforts into the quantification of incidence and the identification of HSR risk factors. With regard to the latter, commonly used platinum agents such as carboplatin (CBDCA) and oxaliplatin (L-OHP) are known risk factors for HSRs [1].

CBDCA is one of the most frequently used platinum agents for the treatment of several malignancies (e.g. head and neck, lung, breast, cervical, ovarian, testicular cancer, and malignant lymphoma). The overall incidence of CBDCA-HSRs can range between 1–44%, with less than 1% occurring within 5 CBDCA cycles, 6.5% in 6 cycles, 27% in 7 or more cycles, and 44% in third-line retreatment [1]. L-OHP, a drug commonly used to treat metastatic colorectal cancer, is generally combined with the genotoxic agent fluorouracil or its analogs. The incidence of L-OHP-related HSRs ranges from 10–18.9%, and usually develops following 6 or more cycles of treatment. Furthermore, the risk of HSRs driven by common platinum agents increases in patients who undergo repeated treatment [2-5].

NDP (cis-diammine-glycolatoplatinum) is a cisplatin (CDDP) analog that has been approved for the treatment of various solid tumors; the drug elicits lower gastrointestinal and renal toxicities when compared with CDDP [6, 7]. Thus, NDP may become the 'drug of choice', and substitute for both CDDP and CBDCA in the treatment of solid cancers. In support of this, several phase 2 studies have demonstrated the efficacy of NDP combination therapy in cervical cancer [8-10] and in head and neck cancer [11-13]. A recent phase 3 study indicated that NDP plus docetaxel was superior to CDDP plus docetaxel with regards to overall survival in advanced or relapsed squamous cell lung cancer patients [14]. Based on this evidence, NDP is currently the third most commonly used platinum agent, with only CDDP and CBDCA being used more frequently in the clinic.

NDP-HSRs can be associated with severe adverse clinical symptoms, although the risk factors that precipitate such events are still unclear. To minimize the risk and maximize the benefit of NDP therapy, it is therefore essential to identify factors associated with NDP-driven HSRs. In many cases, NDP is used to treat patients with gynecologic cancer

who have previously experienced CBDCA-HSRs. However, whether CBDCA treatment history has an impact on the risk of developing NDP-HSRs has not been formally tested. In this retrospective study, we investigated the incidence of NDP-HSRs, searched for associated risk factors, and evaluated the relationship between CBDCA- and NDP-triggered HSRs.

Patients and methods

Study design

This study was a single-center, retrospective cohort study. The study protocol was approved by the ethics board of Nagoya University School of Medicine.

Patients

From April 2011 to July 2015, we identified Japanese patients aged ≥20 years and who received NDP monotherapy at Nagoya University Hospital. Exclusion criteria included prior treatment history with an NDP-containing regimen.

Treatment

In the monotherapy regimen approved by our institution, NDP at 80–100 mg/m^2 was

administrated intravenously for 60 min following pretreatment with 13.2 mg dexamethasone (DEX) and 5-HT_3 antagonist every four weeks. Dose and type of 5-HT_3 antagonist were optional. NDP and DEX dose reduction was allowed depending on each patient's condition.

Hypersensitivity reactions

Considering their delayed onset, we defined HSRs caused by either NDP or CBDCA as allergy-like reactions (including itching, rash, flush, chest tightness, respiratory discomfort, emesis, blood pressure changes, and facial swelling) that occurred within the first 48 h of treatment. We excluded cases that could have been due to other drugs administered concomitantly with platinum reagents. The severity of NDP and CBDCA-HSRs was graded according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE ver.4.0).

Data collection

Clinical data collected from the medical records were as follows: age, type of cancer, history of allergy, incidence and severity of NDP- and CBDCA-HSRs, symptoms of NDP-HSRs, NDP exposure during the study period (total number of courses, doses, and

cumulative dose). We also recorded treatment line number, the number of prior CBDCA administrations, the interval between NDP treatment and any previous platinum treatment (defined as the number of months from the last platinum treatment to the first NDP administration).

Statistical analysis

Univariate analyses were performed by using Mann-Whitney U test, and Fisher's exact test. A multivariate logistic regression analysis was used to estimate adjusted odds ratios. All statistical analyses were performed with the Statistics Program for Social Science version 23 (SPSS Inc., USA). Variables were considered significant when the *p* value was less than 0.05.

Results

Patient characteristics

One patient who had been previously treated with a regimen including NDP was excluded. A total of 111 patients treated with NDP was included. Because gynecologic cancer patients were in the majority, 90 of 111 patients (81%) were female (Table 1).

Median age was 59 years (range, 29–78 years). Eighty-eight of 111 patients (79%) were first treated with CDDP or CBDCA, and given NDP as a third or higher line treatment.

Situations with developing NDP-HSRs

In the study population, 8 patients experienced HSRs following NDP treatment, representing an incidence of 7.2% of all treated patients. Five of 8 NDP-HSRs (63%) were observed within 10 min, and the most frequently observed symptoms were flush (6 patients) and respiratory discomfort (4 patients), which were typical and also observed in CBDCA-HSRs (Table 2) [1, 2]. Two patients needed hospitalization (Grade 3) and another two were transferred to an intensive care unit for treatment of HSRs (Grade 4). Six of 8 patients (75%) developed HSRs during the second NDP cycle (Figure 1). All patients with NDP-HSRs had already been exposed to more than 3 cycles of CBDCA treatment (Table 3). There was no association between HSR grade and the number of platinum cycles. Five of 8 patients (63%) had a history of CBDCA-HSRs.

Risk factors for NDP-HSRs

Univariate analysis revealed three parameters as potential risk factors for NDP-HSRs (Table 3). First, the number of prior CBDCA treatments was significantly higher in

patients with NDP-HSRs compared to patients without NDP-HSRs (median 9.5 vs. 5, p = 0.009). Second, the overall incidence of CBDCA-HSRs was higher in patients with NDP-HSRs relative to patients without NDP-HSRs (63% vs. 6%, $p < 0.001$). Finally, the proportion of patients that received NDP 6 months or more after the previous platinum treatment was higher in patients with NDP-HSRs than patients without NDP-HSRs (88% vs. 43%, p = 0.023). The effects of DEX reduction, age, and the number of NDP cycles had no statistically significant impact on NDP-HSRs.

Using multivariate analysis, NDP-HSRs were significantly associated with two factors: history of CBDCA-HSRs (odds ratio = 37.5, 95% CI = 5.38–262, $p < 0.001$), and the length of the interval between NDP and the previous platinum treatment (odds ratio = 13.9, 95% CI = 1.23–158, p = 0.034) (Table 4).

Association of NDP-HSRs with CBDCA-HSRs

In patients who experienced CBDCA-HSRs, 5 of 11 individuals (45%) developed NDP-HSRs. The interval between the first NDP treatment and previous CBDCA-HSRs was significantly longer in this group than in patients without NDP-HSRs (median months, 30 vs. 1, p = 0.025) (Table 5). Additionally, in the study population, 72 of 111

patients had the history of CBDCA treatment (Table 1). The incidence of NDP-HSRs was significantly higher in these 72 patients compared to those without CBDCA-HSRs (45% vs. 4.9%, $p > 0.001$) (Table 6).

Discussion

In our study, most of NDP-HSRs occurred during early cycle of treatment, in contrast that the risk of common platinum-HSRs increased in patients who undergo repeated treatment. NDP is commonly used as the third platinum agent. It is predicted that prior repeated platinum exposure influence early-onset of NDP-HSRs.

Additionally, we found that a history of CBDCA-HSRs was the most significant risk factor for NDP-HSRs.

Various mechanisms have been proposed to explain platinum-dependent HSRs. First, there is a correlation between severe CBDCA-HSRs and IgE-dependent-HSRs. Patients with CBDCA-HSRs had significantly higher expression of the Fc fragment of IgE receptor-I (Fc ε RI) on basophils, and a higher level of Fc ε RI mRNA in peripheral blood compared to patients without CBDCA-HSRs. Accordingly, it was suggested that

monitoring the pharmacodynamic changes of Fc ε RI expression on basophils was essential for prevention of CBDCA-HSRs in high-risk patients [15].

Second, specific IgE (sIgE) was observed in several patients with CBDCA- or L-OHP-induced HSRs; this has led to the proposal that sIgE may recognize different epitopes in CBDCA and L-OHP. CBDCA sIgE may be directed against primary amine groups present on both CBDCA and CDDP, but which are absent on L-OHP [16]. Similar to CBDCA, NDP also contains a primary amine group, and may therefore be recognized by autoantibodies. Together, these observations suggest that platinum-driven HSRs develop due to activation of a type I allergy mechanism, and NDP possibly cross-reacts with CBDCA as to HSRs.

While our multivariate analysis indicated that a history of CBDCA-HSRs was a risk factor for NDP-HSRs, substituting CBDCA with NDP in women with gynecologic cancers who experienced CBDCA-HSRs is an effective treatment strategy. Indeed, two groups have reported approximately 30–35% response rates, including five cases of complete response [17, 18]. Accordingly, NDP treatment in patients who had experienced CBDCA-HSRs should generally be avoided, except when significant benefits are

expected.

A long interval between NDP treatment and any previous platinum regimen was also detected as a risk factor for NDP-HSRs. This is consistent with a previous report that a 12-month platinum-free interval is a risk factor for CBDCA-HSRs in gynecologic cancer patients [3, 19]. Similarly, L-OHP salvage therapy is a risk factor for HSRs in colon cancer patients [20]. In addition, two previous studies have also reported incidence of NDP-HSRs and interval to re-challenge after CBDCA-HSRs. Michikami *et al*, Arimoto *et al*, and we have reported that incidence of NDP-HSRs after CBDCA-HSRs were 7.9% in patients subsequently switched NDP, 27% in patients with 1.4 months of interval to re-challenge, and 45% in patients with 9 months (Table 5) [17,18]. Incidence of NDP-HSRs after CBDCA-HSRs was increased associated with long interval to re-challenge. These reports suggest that the development of immune sensitization to platinum agents, including NDP, requires a relatively long period before it manifests in the form of clinical symptoms. Our current results suggest that a long time interval may be required to develop cross-immune sensitization to NDP in patients with CBDCA-HSRs. Thus we infer that, when deemed necessary, NDP treatment should be

initiated relatively quickly after CBDCA treatment in those patients who experienced CBDCA-HSRs. Conversely, if a long period (> 6 months) has elapsed since the last episode of CBDCA-HSRs, NDP should only be administered with especially careful monitoring. However, further studies are required to validate this approach, because many mechanistic aspects of platinum immune sensitization remain unclear.

Management for platinum-HSRs including premedication, desensitization and substitution of platinum agents have been researched [1,21-24]. However, preventive effects are still limited, and specific prophylaxis for NDP-HSRs has scarcely been reported. Perhaps, subsequent substitution of NDP for CBDCA is effective management for CBDCA-HSRs, but further study is also needed to demonstrate this hypothesis.

Several limitations of this study should be noted. As it was retrospective, this study was not able to address the outcome of novel changes to treatment strategies when HSRs were encountered. Also, the number of study subjects was relatively small and the data presented should therefore be interpreted with caution. Additionally, we only focused on prediction of NDP-HSRs development, so we didn't evaluate efficacy of therapy and HSRs prophylaxis.

In conclusion, a history of CBDCA-HSRs and an interval of 6 months or greater between NDP and the previous platinum treatment are risk factors for NDP-HSRs. Thus, NDP monotherapy in patients who have experienced CBDCA-HSRs should be implemented with great care. When benefit of the NDP monotherapy is expected for patients in whom the interval between different platinum treatments is long, its administration should be carefully monitored.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Tables

Table 1: Patient characteristics

Table 2: Summary of individual cases with NDP-HSRs

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Table 5: Summary of patients with CBDCA-HSRs

Table 6: Subgroup analysis in patients with a history of CBDCA treatment

Figure captions

Fig1 Number of NDP cycles in patients with NDP-HSRs. Six of eight NDP-HSRs developed in the second NDP cycle

Table 1 Patient characteristics

	Patients (n = 111)
Age (years)	
median	59
range	29-78
Sex	
male	21
female	90
Number of NDP cycles	
median	3
range	1-16
History of CBDCA treatment	
yes	72
no	39
Type of cancer	
gynecologic	88
head and neck	20
others	3
Line of therapy	
first or second	23
third or higher	88

NDP : nedaplatin, CBDCA : carboplatin

Table 2 Summary of individual cases with NDP-HSRs

No.	NDP-HSRs	CBDCA-HSRs	Onset of NDP-HSRs, min	Symptoms
1	Gr 1	Gr 1	7	flush, hyperemia
2	Gr 2	Gr 2	5	flush, respiratory discomfort
3	Gr 2	-	3	flush, hyperemia,
4	Gr 2	Gr 3	< 60	flush
5	Gr 3	Gr 3	23	respiratory discomfort, itching
6	Gr 3	-	35	flush, nausea, edema
7	Gr 4	-	9	respiratory discomfort, hypotension, consciousness disorder, itching
8	Gr 4	Gr 3	9	flush, respiratory discomfort, hypotension, consciousness disorder

NDP : nedaplatin, CBDCA : carboplatin, HSRs : hypersensitivity reactions

Table 3 Results of univariate analysis.

	NDP-HSRs (+) (n = 8)	NDP-HSRs (-) (n = 103)	*p* value
Age (years)			
median	53.5	59	0.523 [a]
range	38-71	29-78	
Number of NDP cycles			
median	2	3	0.097 [a]
range	2-7	1-16	
Number of prior CBDCA treatments			
median	9.5	5	0.009 [a*]
range	3-28	0-29	
Type of cancer			
gynecologic	8	80	
head and neck	0	20	
others	0	3	
History of CBDCA-HSRs	63% (5/8)	6% (6/103)	< 0.001 [b*]
Interval between NDP administration and the previous platinum treatment (months)			
> 6	88% (7/8)	43% (44/103)	0.023 [b*]
DEX reduction	63% (5/8)	42% (43/103)	0.289 [b]

NDP : nedaplatin, CBDCA : carboplatin, HSRs : hypersensitivity reactions, DEX : dexamethasone

NDP-HSRs (+) : Patients with NDP-HSRs, NDP-HSRs (-) : Patients without NDP-HSRs

[a] Mann-Whitney U test, [b] Fisher's exact test, [*] $p < 0.05$

Table 4 Results of multivariate analysis

Factors	Odds ratio	95% CI	*p* value
History of CBDCA-HSRs	37.5	5.38 – 262	< 0.001*
Interval between NDP administration and the previous platinum treatment (months)			
> 6	13.9	1.23 – 158	0.034*

NDP : nedaplatin, CBDCA : carboplatin, HSRs : hypersensitivity reactions, CI : confidence interval

* $p < 0.05$

Table 5 Summary of patients with CBDCA-HSRs

	NDP-HSRs (+) (n = 5)	NDP-HSRs (-) (n = 6)	Total (n=11)	*p* value
Interval between the first NDP treatment and CBDCA-HSRs (months)				
median	30	1	9	0.025 [a*]
range	9-33	1-27	1-33	

NDP : nedaplatin, CBDCA : carboplatin, HSRs : hypersensitivity reactions

NDP-HSRs (+) : Patients with NDP-HSRs, NDP-HSRs (-) : Patients without NDP-HSRs

[a] Mann-Whitney U test, * $p < 0.05$

Table 6 Subgroup analysis in patients with a history of CBDCA treatment.

	CBDCA-HSRs (+) (n = 11)	CBDCA-HSRs (-) (n = 61)	*p* value
Age (years)			
median	57	55	0.424 [a]
range	44-77	29-78	
Number of prior CBDCA treatments			
median	12	7	0.003 [a*]
range	8-28	1-29	
Number of NDP cycles			
median	2	3	0.811 [a]
range	2-13	1-16	
NDP-HSRs development	45% (5/11)	4.9% (3/61)	< 0.001 [b*]

NDP, nedaplatin; CBDCA, carboplatin; HSRs, hypersensitivity reactions

CBDCA-HSRs (+) : Patients with CBDCA-HSRs, CBDCA-HSRs (-) : Patients without CBDCA-HSRs

[a] Mann-Whitney U test, [b] Fisher's exact test, * $p<0.05$

Figure

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