

Hypersensitivity Reactions Associated with Platinum-containing Antineoplastic Agents for Thoracic Malignancies

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Abstract. Recently, the use of platinum-containing antineoplastic agents for extended periods has increased. In this study, we determined the relationship between the hypersensitivity reactions to cisplatin or carboplatin and the frequency of administration among patients with thoracic malignancies. The study included 255 patients with thoracic malignancies who were treated with chemotherapy containing cisplatin or carboplatin in our institution between April 2007 and October 2008. A total of 89 patients received a median of 3 courses of cisplatin and 140 patients a median of 4 courses of carboplatin. A median of 6 courses of cisplatin plus carboplatin was administered to a further 26 patients. The total incidence of hypersensitivity reactions was 1.96%. Patients who were treated with <6 courses of platinum-containing antineoplastic agent did not experience any hypersensitivity reaction, but one patient, who was administered with 6 courses of platinum-containing antineoplastic agent experienced a hypersensitivity reaction (0.44%), as did four patients who were administered ≥ 7 courses (13.8%). Univariate and multivariate analyses indicated that the number of courses of platinum-containing antineoplastic agents was significantly correlated to the incidence of hypersensitivity reactions to these agents.

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Cisplatin and carboplatin, which are platinum-containing antineoplastic agents, are primarily used as first-line therapy for patients with thoracic malignancies. Recently, various regimens of platinum-containing antineoplastic agents have been developed, as well as a variety of supporting therapeutic options (1-4). As a result, the number of cases in which platinum-containing antineoplastic agents are used for an extended period is increasing. In fact, in our institution, most patients with non-small cell lung cancer (NSCLC) who receive outpatient chemotherapy are treated with non-platinum monotherapy until disease progression, and many patients receive long-term chemotherapy comprising of multiple cycles and regimens, as we believe that long-term chemotherapy might prolong survival regarding thoracic malignancies (5).

Platinum-induced hypersensitivity reactions are a potentially fatal complication, the incidence of which is increasing due to the growing use of platinum-containing antineoplastic agents in chemotherapy. However, in the treatment of thoracic malignancies, hypersensitivity to platinum-containing antineoplastic agents has rarely been studied. In this study, we retrospectively examined the relationship between hypersensitivity reactions to platinum-containing antineoplastic agents and frequency of administration among patients with thoracic malignancies treated with cisplatin or carboplatin.

Patients and Methods

The study included 255 patients with thoracic malignancies who were administered chemotherapy containing cisplatin or carboplatin at our institution between April 2007 and October 2008. Previous reports have indicated that the symptoms of a hypersensitivity reaction to platinum-containing antineoplastic agents occur from several minutes to several days after administration of the agents (6-

Table I. Platinum course number for initial hypersensitivity reaction to platinum antineoplastic agents.

No. of course	Reaction (n)		Total	Incidence (%)
	Yes	No		
<6	0	205	205	0
6	1	21	22	4.5
7	0	7	7	0
8	0	7	7	0
9	1	3	4	25
10	1	2	3	33.3
11	0	4	4	0
≥12	2	2	4	50
Total	5	250	255	1.96
<7	1	225	226	0.44
≥7	4	25	29	13.8

8). In this study, moderate or severe symptoms (grade 3, 4) occurring immediately after administration of cisplatin or carboplatin were defined as hypersensitivity reactions, according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)(<http://www.jcog.jp>). Hypersensitivity reactions that occurred within the first 10 minutes following the infusion of taxanes were excluded in order to exclude the influence of hypersensitivity to taxanes.

R ver. 2.8.1 software (available at <http://www.R-project.org>; R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Variables included in the analysis were gender, age, diagnosis (lung cancer or malignant mesothelioma), number of courses of platinum-containing antineoplastic agents, and the type of platinum-containing antineoplastic agent administered. With reference to a previous report, we decided to divide the patients into groups based on their receipt of <7 or ≥7 courses of platinum-containing antineoplastic agent (6). Furthermore, we evaluated whether the hypersensitivity reactions that occurred were due to carboplatin or cisplatin. When both drugs were administered, the responsible drug was identified based on our experience for each type of reaction. However, we excluded the type of platinum-containing antineoplastic agent from the multivariate analysis since it was impossible to determine when both drugs were used.

Univariate and multivariate analyses were performed with a χ^2 test and Fisher's exact test. A *p*-value <0.05 was considered statistically significant.

Results

A total of 255 patients (198 men and 57 women) were included in the study. Their median age was 65 years (range, 29-82 years). The histological classification was NSCLC in 186 cases, small-cell lung cancer (SCLC) in 54 cases, and malignant mesothelioma in 15 cases. A total of 89 patients received a median of 3 courses (range, 1-14) of cisplatin, and 140 patients, a median of 4 courses (range,

Table II. Univariate analysis (n=255).

Factor	Hypersensitivity			<i>p</i> -Value	
	No.	negative	positive	Univariate	Multivariate
Age (years)					
≤65	139	136	3	0.838	0.903
>65	116	114	2		
Gender					
Male	198	195	3	0.678	0.307
Female	57	55	2		
Diagnosis					
Lung cancer	240	236	4	0.693	0.403
Mesothelioma	15	14	1		
Platinum courses (n)					
<7	226	225	1	<0.0001	0.002
≥7	29	25	4		
Platinum agent					
Cisplatin	89	88	1		
Carboplatin	140	136	4	0.685	
Both	26	26	0		

1-18) of carboplatin. A median of 6 courses (range, 2-11) of cisplatin plus carboplatin were administered to 26 patients.

The median number of platinum courses administered was 10 (range, 6-18). The total incidence of hypersensitivity reactions was 1.96%. One patient treated with <7 courses of platinum-containing antineoplastic agent experienced a hypersensitivity reaction (0.44%), whereas four patients administered ≥7 courses experienced hypersensitivity reactions (13.8%) (Table I). All five of these patients experienced flushing, dyspnea, hypotension, and symptomatic bronchospasm within 10 min of the injection of the platinum-containing antineoplastic agent. In these cases, we immediately discontinued treatment and initiated supportive therapy (corticosteroids, oxygen, and intravenous fluids). Although the symptoms improved among all cases within one day, we did not undertake any rechallenge.

According to the univariate and multivariate analyses, age, gender, diagnosis, and type of platinum-containing antineoplastic agent did not differ significantly between the groups. However, between patients administered <7 and ≥7 courses of platinum-containing antineoplastic agent, hypersensitivity reactions to the agents were significantly more common (univariate analysis: *p*<0.0001, multivariate analysis: *p*=0.002) (Table II).

Discussion

Severe hypersensitivity reactions to platinum-containing antineoplastic agents are rare in thoracic malignancies. Therefore, the incidence of mild-to-moderate reactions may

be underestimated, even though hypersensitivity reactions are a potentially fatal complication. Previously, the overall incidence of hypersensitivity to cisplatin has been reported as 5-20% and of hypersensitivity to carboplatin as 1-44% (9). Hypersensitivity reactions to cisplatin and carboplatin are rarely observed during the first course of treatment; in fact, most allergic reactions are reported after the patient has received a significant number of treatments, even though the patients do not display any hypersensitivity symptoms up to that point (6, 7, 9-12). In our study, all hypersensitivity reactions to platinum-containing anti-neoplastic agents occurred after administration of more than 6 courses. It was necessary to closely monitor patients immediately after infusion of the platinum-containing antineoplastic agents because all the hypersensitivity reactions occurred within minutes or days of the initiation of the infusion.

The prolonged period of sensitization and the rapid onset of symptoms supports the role of a type I immunoglobulin (Ig) E-mediated mechanism, and a few studies provide evidence to support this (13, 14). On the other hand, other mechanisms may also be active, such as non-immunological histamine release (15). Thus, the mechanism of hypersensitivity reactions to platinum-containing anti-neoplastic agents remains unclear.

Hypersensitivity reactions to platinum-containing anti-neoplastic agents and taxanes (paclitaxel and docetaxel) differ in their timing and mechanism (10). In fact, nearly 95% of all reactions to taxanes occur during the first or second infusion, suggesting a non IgE-mediated mechanism to be present (16, 17).

Recently, survival and quality of life among patients with thoracic malignancies have improved because of developments in supportive care and the use of pemetrexed and molecular-targeted drugs. However, the frequency of administration of platinum-containing antineoplastic agents is increasing because thoracic malignancies are generally treated with weekly paclitaxel/carboplatin and concurrent radiation therapy (18), weekly paclitaxel/carboplatin (19, 20), or platinum-based doublet chemotherapy for patients who have already been treated with a platinum agent (21). Thus, it is surmised that the development of hypersensitivity reactions will increase along with the increased use of platinum-containing antineoplastic agents.

A previous study showed that a reactive skin test is effective in predicting and thus reducing the incidence of platinum-induced hypersensitivity reactions (16). However, at present, a reactive skin test is not widely used before chemotherapy to avoid the risk of skin ulceration. The risk of severe hypersensitivity reactions to platinum-containing antineoplastic agents can potentially be reduced by checking for a history of drug allergies, adequate premedication, careful patient monitoring, and prompt intervention when signs of hypersensitivity occur (13).

Conclusion

For patients who require numerous courses of platinum-containing agents, it is necessary to perform a thorough examination and interview before initiating treatment in order to facilitate rapid detection of any hypersensitivity reaction that may occur during the treatment period.

Conflict of Interest Statement

The Authors have no financial arrangements or relationships with any individuals or organizations that could potentially influence their work.

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