

Retrospective study of hypersensitivity reactions to chemotherapeutic agents in a thoracic oncology service

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Summary

What is known and objective: With the increasing use of cancer chemotherapy agents, hypersensitivity reactions are commonly encountered. The allergic clinical symptoms are variable and unpredictable. The aim of this study was to identify the characteristics of hypersensitivity reactions and to assess the value of skin tests for platinum salts and pemetrexed in the treatment of patients with non-small cell lung cancers or malignant pleural mesothelioma.

Methods: A single-centre retrospective study was performed for 2 years. Patients treated with the drugs of interest for an advanced or metastatic non-small cell lung cancers or malignant pleural mesothelioma and who experienced hypersensitivity reactions symptoms were eligible for this study. Clinical symptoms of hypersensitivity reactions, population characteristics and administered chemotherapy regimens were identified.

Results: The hypersensitivity reactions frequency was rare (1.2%) and concerned 17 patients in our study. Typical clinical features of immediate hypersensitivity reactions associated with treatment were observed for nine patients (anaphylactic reactions for three cases, angioedema and hypotension associated with asthenia and heat in one case, respectively, and other cutaneous symptoms in the remaining four cases). Skin tests were positive in three patients, but only for platinum salts. The outcome after reintroduction of a negatively tested platinum salt allowed us to calculate a negative predictive value for platinum salt skin tests of 100%. For pemetrexed, skin tests were negative for all patients.

What is new and conclusion: Skin tests could be used to diagnose hypersensitivity reactions with platinum salts or to evaluate the possibility of cross-reactions between two platinum salts. A negative skin test may predict with reasonable reliability the absence of future hypersensitivity reactions in case of reintroduction of drug infusion. Because the IgE-mediated mechanism has never been demonstrated for pemetrexed, skin tests are not valid and have no diagnostic value for this molecule. Because hypersensitivity reactions are potentially fatal adverse events, we recommend that patients who experience a hypersensitivity reactions onset should be monitored closely and clinicians must be aware of hypersensitivity reaction signs.

KEYWORDS

anaphylaxis, drug hypersensitivity, lung cancer, platinum salts, skin tests

1 | WHAT IS KNOWN AND OBJECTIVE

Lung cancers and malignant pleural mesothelioma are two aggressive thoracic malignancies associated with significant mortality. Non-small cell lung cancers (NSCLC) represent more than 80% of lung cancers, and approximately 70% of patients are diagnosed in an advanced stage of the disease, often inoperable or metastatic.^{1,2} Despite recent diagnostic and therapeutic advances, the prognosis remains poor, with the 5-year observed survival rate being about 10% for lung cancer and 7% for malignant pleural mesothelioma.³⁻⁵

First-line therapy usually consists of a combination of a platinum salt (cisplatin or carboplatin) with a third-generation agent (docetaxel, paclitaxel, gemcitabine, vinorelbine or pemetrexed). Due to its efficacy and a good safety profile, pemetrexed may be preferable to other agents for patients with non-squamous NSCLC.^{1,6} Moreover, the combination of pemetrexed and cisplatin was shown to induce high response rates for malignant pleural mesothelioma.⁷

Because of the increasing use of cancer chemotherapy agents in clinical practice, hypersensitivity reactions (HR) are commonly encountered. During the first five cycles, there is approximately a 1% risk of HR. With an increase in the number of cycles, the risk of HR increases, ranging from 27% in patients receiving more than seven cycles of treatment to 44% in the third-line retreatment setting. Cisplatin HR exhibit similar characteristics and range from 5% to 20%, and increase with concomitant radiation.⁸⁻¹³

Allergic clinical symptoms are variable and unpredictable. Systemic reactions, skin toxicities including eczema, urticaria, pruritus, and erythema, or more serious effects, such as bullous skin lesions, angioedema or anaphylaxis, can occur.¹²⁻¹⁹ HR symptoms may begin during infusion or within minutes to days after IV administration, even though the same substance is administered to the same patient.^{11,13,20} When allergic clinical symptoms appear after multiple infusions, type I hypersensitivity mediated by IgE immunoglobulin is suspected. Other mechanisms, such as type IV hypersensitivity mediated by CD4+ T cells, also seem to be involved.¹³

To diagnose and prevent drug HR risk, skin tests (ST) have been developed. They are based on the use of prick tests and intradermal tests described by the World Allergy Organization.²¹ ST with platinum agents have previously been reported in the literature, especially in the management of gynaecological or gastrointestinal cancers, with those patients treated for relapsed disease being at greater risk of experiencing a HR after prior exposure to platinum chemotherapy.^{12,22-25} However, they have not been clearly evaluated for patients with lung cancer. Moreover, although pemetrexed is one of the most commonly prescribed agents, ST for this compound have not yet been described, even though cases of anaphylaxis have previously been published.^{10,26}

To optimize NSCLC or mesothelioma management for patients with HR onset, ST for platinum salts and pemetrexed are performed in our University Teaching Hospital. The aim of this study was to identify HR characteristics and to assess the value of platinum salts and pemetrexed ST; a positive result would confirm the responsibility of the platinum salt or pemetrexed in HR.

2 | METHOD

2.1 | Ethical approval

Approval was obtained from the "Société de Pneumologie de Langue Française" ethics committee (CEPRO 2016-019).

2.2 | Design and setting

A single-centre retrospective study was performed for 2 years. Retrospective identification of patients referred by an oncologist to an allergist for the administration of ST was possible by the prescription of ST protocols in CHIMIO[®] software (Computer Engineering, Paris, France). After identification of these patients, clinical data (including symptoms of HR, identification of a greater risk of developing a HR, eg adherence to premedication, previous allergic reactions, atopic disease) and history of cancer treatment were collected from the institutional patient database and CHIMIO[®] software (Computer Engineering).

2.3 | Patients

Those eligible for this study were patients treated for an advanced or metastatic NSCLC or malignant pleural mesothelioma with cisplatin- and carboplatin-based doublet chemotherapeutic regimens, or a second-line therapy with pemetrexed alone, who experienced HR symptoms and were referred by a medical oncologist to undergo ST in the Respiratory and Allergy Department. Patients involved in clinical trials were excluded. Clinical inclusion criteria were skin toxicity (including eczema, urticaria, pruritus, rash, erythema, hives, conjunctivitis, bullous eruption and oedema), bronchospasm, hypotension or an anaphylactic shock.

2.4 | Skin tests

Skin tests were conducted in accordance with the European Academy of Allergy and Clinical Immunology (EAACI) position paper.²⁷ Skin prick tests were administered on the volar side of the forearm with a pure injectable preparation of each antineoplastic agent (cisplatin, injectable form, 1 mg/mL from Mylan laboratory, USA; carboplatin injectable form, 10 mg/mL from Teva laboratory, Israel; pemetrexed, powder for intravenous infusion, 500 mg from Lilly laboratory, USA), using a saline solution containing 0.9% and 9% codeine phosphate, respectively, as negative and positive controls. Positive results were defined by the appearance of a 3-mm or larger wheal within 20 minutes.

Intradermal tests (IDTs) were administered on the patients' forearm by injecting 0.02-0.04 mL of each sterile dilution.²² IDT reactions were considered positive when the size of the initial wheal increased by a minimum 3 mm in diameter after 15-20 minutes. The wheals were examined again at 24 and 48 hours. When prick tests were strongly positive, IDTs were not performed. IDTs were prepared using a sterile solution of each molecule, sequentially diluted in 0.9% saline as previously described.¹² The syringe kits (capacity 1 mL, Becton, Dickinson and Company, USA) containing each dilution included the following:



four syringes containing pure product and successive dilutions 10^{-1} , 10^{-2} , 10^{-3} for platinum salts; and five syringes containing pure product and successive dilutions 10^{-1} , 10^{-2} , 10^{-3} , 10^{-4} for pemetrexed.

These dilutions were prepared 1 hour before injection in a centralized unit for cytotoxic drugs in a 500 4S isolator (JCE Biotechnology, France).

3 | RESULTS AND DISCUSSION

From January 2011 to July 2013, 17 patients with HR clinical signs were enrolled. In our study, 1.2% of patients treated for an advanced or metastatic NSCLC or a malignant pleural mesothelioma with cisplatin- and carboplatin-based doublet chemotherapeutic regimen, or a second-line therapy with pemetrexed alone in the Thoracic Oncology Service experienced a HR onset. Based on the French scoring system, the likelihood of each chemotherapeutic agents' involvement was determined.²⁸ In nine cases, HR symptoms began within the first hour after initiation of infusion and platinum salts were suspected to be responsible for the HR. Pemetrexed was suspected to be involved in five delayed reactions. For four patients, the French scoring system did not allow the identification of which drug between platinum salts or pemetrexed was responsible for the HR onset.

Typical clinical features of immediate HR associated with treatment were observed in all nine patients who experienced immediate HR (anaphylactic reactions for three cases, angioedema and hypotension associated with asthenia and heat in 1 case, respectively, and other cutaneous symptoms in four cases) (Table 1). None of these 17 patients had an obvious greater pretreatment risk of developing a HR. For platinum salt and pemetrexed, the median number of courses administered until a reaction occurred was two cycles (range: 1; 4) and 2.5 cycles (range: 1; 22), respectively.

ST were performed in 15 of 17 patients of our study. For one patient (patient 11), ST were not administered because of current corticosteroid therapy and one patient (patient 4) did not make the appointment. Ten patients were concomitantly tested for several molecules. The median time between HR onset and conduct of the tests was 4 weeks (range: 2 to 104 weeks).

ST were positive in three patients, but only for platinum salts. In these three patients with positive ST, three IDTs were positive at dilution 10^{-1} for cisplatin and one IDT was positive at 10^{-2} for carboplatin. These IDTs were positive in immediate reading at 20 minutes. Among the nine patients with typical symptoms of immediate HR, three patients (patient 1, 2, 5) had positive IDTs with platinum salts. For patients who developed delayed HR, all the IDTs administered were negative in the immediate reading but one IDT for pemetrexed was doubtful for one patients (patient 6) in delayed reading 24 hours later.

Cisplatin and carboplatin were simultaneously tested in nine patients to rule out cross reaction when a platinum salt is substituted by another. One case of cross-hypersensitivity was detected (patient 5) leading to the interruption of the chemotherapy. For two patients with positive IDTs to cisplatin (patients 1, 2) and negative IDTs to carboplatin, the substitution of the platinum salt was decided. No adverse drug

reaction was observed, and cytotoxic treatment could be continued. The outcome after reintroduction of a negatively tested platinum salt allowed us to calculate a negative predictive value for platinum salt ST of 100%. The positive predictive value could not be calculated, because the reintroduction of platinum salt in a patient with suspected cross-reactivity was considered as being unethical. For four patients (patients 7, 8, 10, 12), platinum salt was discontinued even though IDTs were negative, because of initiation of a maintenance therapy or prescription of different chemotherapy regimens for tumour escape.

Concerning pemetrexed, treatment was discontinued in four of nine patients and this treatment was maintained for three patients until disease progression. Reintroduction of pemetrexed was not possible for two patients (patients 15 and 17) because of different chemotherapy protocols for tumour escape or death. One patient (patient 6) experienced recurrence of a mild HR with similar symptoms to the first onset. Two years later, a protocol based on carboplatin and paclitaxel was used for the treatment of lung cancer progression for this patient and no adverse drug reaction was observed (Table 1).

The HR rate in our study was similar to those previously described.^{8-13,29} Among the main identified risk factors of HR, a treatment combining carboplatin and paclitaxel, a prior platinum treatment based on the administration of six cycles of platinum salts, and an interval without carboplatin >13 months, has been suspected.^{8,13,15} Although the carboplatin/paclitaxel protocol can be used to treat lung cancer, this protocol is not the first therapeutic choice in our hospital (less than 10% of patients treated over the period of the study). For advanced/metastatic NSCLC care, the most commonly prescribed treatment is a combination of cisplatin or carboplatin and pemetrexed during four cycles, followed by a maintenance treatment without platinum salt. All patients in the study experienced HR during their first-line chemotherapy. None received an initial course of platinum-based doublet chemotherapy or an extended chemotherapy break. Patients therefore did not reach six platinum salts cycles.

In our study, cutaneous manifestations or angioedema developed in 12 of 17 patients. This result is very similar with HR symptoms described in the literature, which are firstly cutaneous manifestations, including pruritus, urticarial and erythema, or more severe toxicity (such as bullous eruptions) representing about 75% of HR symptoms.^{11-13,29-31} Anaphylactic shock occurred for three of 17 patients in our study and two of 21 patients in a previous study¹² and, for one case, pemetrexed was the molecule suspected (Table 2).

The exact mechanism of cytotoxic agents' allergy remains unclear, but type I and type IV hypersensitivity are suspected.¹³ Early cutaneous symptoms of HR or anaphylactic reaction are frequently attributed to a type I hypersensitivity. It is characterized by an immediate reaction to an allergen upon second contact. During the first exposure to an allergen, the immune system stimulates B cells, which then synthesize IgE. The IgE migrates through the body and inserts into mast cells. On the second exposure, the allergen binds to the IgE immunoglobulin, causing the degranulation of mast cells associated with the release of histamine, leukotrienes and prostaglandins. This mechanism has been largely described for HR with platinum agents.^{11-13,20,22,32}

TABLE 1 Reactions to cytotoxic clinical features, and IDTs results in the study population

Patient	Suspected molecule	Number of cycles after which the HR occurred	IDT		Delay	Clinical features	Treatment change/Continuation/Stop
			Substance tested	Results			
1	CDDP/PEM	2	CDDP CBDCA	+ –	5 min after initiation of infusion	Anaphylactic reaction with heat, generalized burning, erythema, O2 desaturation	CBDCA/PEM
2	CDDP/PEM	3	CBDCA CDDP	– +	15 min after initiation of infusion	Cutaneous symptoms: itching, erythema	CBDCA/PEM/ Bevacizumab
3	CDDP/PEM	2	CBDCA CDDP	– –	<15 min after initiation of infusion	Cutaneous symptoms: hives, rash, pruritus, pharyngeal oedema and eyelids	CBDCA/PEM/ Bevacizumab
4	CBDCA/PEM	1	CBDCA PEM	ND ND	30 min after initiation of infusion	Cutaneous symptoms: bullous eruption which resolved within 7 days	CBDCA/Navelbine
5	CBDCA/PEM	2	CBDCA CDDP	+ +	30 min after initiation of infusion	Angioedema	Stop
6	CDDP/PEM	1	CBDCA PEM CDDP	– Unclear –	>48 h after the end of the infusion	Cutaneous symptoms: itching, erythema	Stop after 1 more infusion of PEM/ CDDP. 2 years later: CBDCA/PXL following lung cancer progression
7	CBDCA/PEM	1	CBDCA PEM	– –	>48 h after the end of the infusion	Cutaneous symptoms: itching	Bevacizumab/PXL Clinical Trial
8	CDDP/PEM	4	CBDCA CDDP	– –	15 min after initiation of infusion	Systemic signs: asthenia, heat, nausea, hypotension	PEM
9	CDDP/PEM	1	CBDCA CDDP	– –	5 min after initiation of infusion	Anaphylactic reaction with hypotension, stunning pulse peripherally, O2 saturation <60% and delayed hives	CBDCA/PXL
10	CDDP/DTX	4	CBDCA CDDP	– –	30 min after initiation of infusion	Cutaneous symptoms: itching	DTX
11	CBDCA/PXL	3	CBDCA	ND	45 min after initiation of infusion	Anaphylactic reaction with heat, rash, dyspnoea, and hypotension	PEM
12	CDDP/PEM	4	CBDCA CDDP PEM	– – –	10 h after the end of the infusion	Cutaneous symptoms: erythema	Bevacizumab/PEM
13	PEM	1	PEM	NR	>24 h after the end of the infusion	Systemic signs of rhino conjunctivitis	NR
14	PEM	22	PEM	–	> 24 h after the end of the infusion	Cutaneous symptoms: erythema, oedema subeyelid, rhino conjunctivitis	PEM

(Continues)

TABLE 1 (Continued)

Patient	Suspected molecule	Number of cycles after which the HR occurred	IDT		Delay	Clinical features	Treatment change/Continuation/Stop
			Substance tested	Results			
15	CDDP/PEM	1	PEM	-	>24 h after the end of the infusion	Cutaneous symptoms: itching, erythema	CDDP/DTX Clinical Trial
16	PEM	4	PEM	-	6 days after the end of the infusion	Cutaneous symptoms: itching,	PEM
17	PEM	10	PEM	-	5 days after the end of the perfusion	Cutaneous symptoms: painful generalized pruritus	Stop

CBDCA, Carboplatin; CDDP, cisplatin; PEM, pemetrexed; ND, not done, NR, unknown; CS, corticosteroid.

For delayed HR, an IgE-mediated mechanism has not been described. Delayed onset of clinical manifestations (more than 48 hours) and clinical symptoms marked by the occurrence of cutaneous signs suggest a type of cell-mediated response based on Gell and Combs classification. In our study, pemetrexed was suspected for eight cases of delayed HR. To our knowledge, no mechanism to explain these HR has been clearly established. However, results of IDTs do not allow us to attribute the occurrence of these HR to pemetrexed, even though this molecule was suspected.

Although the interest of ST for chemotherapeutic agents has previously been described, their value has not been yet clearly established.²⁹ ST were mainly used to recognize patients without a history of HR but who were at risk to develop a HR onset (as an example, women with gynaecological cancer who have previously received more than six cumulative cycles of platinum salt). Platinum salts IDTs were positive in three patients tested after an episode of immediate HR and none of the three patients tested after an episode of delayed HR. The negative predictive value of our platinum salt ST is similar to previous report, ranging from 0.985 to 0.99.^{15,22} Negative ST are a reliable indicator for a safe rechallenge, but a negative ST do not rule out the risk that HR could still occur because of a low false negative rate, especially for carboplatin (1.5%-8.5%).^{11,13,22,24,25,33} However, obtaining a positive ST remains significant and must be considered.²⁹

For pemetrexed, ST were negative for all the patients after an episode of delayed HR, even though one IDT was doubtful in the delayed reading. However, because the IgE-mediated mechanism has never been demonstrated for pemetrexed, ST are not valid and have no diagnostic value.

In our study, the short time between the onset of symptoms and the performance of ST may explain the relatively low rate of positive ST. Indeed, for IgE immunoglobulin-mediated hypersensitivity, a 4 to 6 weeks' delay is recommended to perform ST.^{12,34} Because the chemotherapy had to be continued, ST were performed few days after the disappearance of HR symptoms. This shorter than recommended delay could be responsible for these results.^{33,35}

We recognize that our study is subject to some limitations. First, we choose a retrospective study because HR frequency is rare, so we needed retrospective observational analysis of large databases to collect information from all the patients treated for an advanced or metastatic NSCLC or malignant pleural mesothelioma. With such a small number of patients, this study may warrant investigation in a larger prospective study.

4 | WHAT IS NEW AND CONCLUSION

Because HR are potentially lethal, early identification and evaluation of symptoms suggestive of HR, prompt discontinuation of infusion and use of appropriate emergency medications aimed at reducing morbidity and risk of fatality, are important.²⁹

ST are not routinely performed.¹³ However, they could be used to diagnose a HR with platinum salts or to evaluate the possibility of cross-reactions between two platinum salts.^{13,22,36} In case of platinum

TABLE 2 HR incidence and severity induced by chemotherapy^{13,29,37}

Molecule	Incidence	Delay	Most common symptoms
Cisplatin	5%-20%	A few minutes or days after cisplatin administration	Rash, fever, erythema, bronchospasm, hypotension
Carboplatin	1%-44% <1% if between cycle 1-5 27% in cycle 7 or more	A few minutes (30 min) or less than 3 days after carboplatin administration, mostly after 6 cycles of chemotherapy	Eczema, urticaria, pruritus, rash, itching, erythema, hives, conjunctivitis, bullous eruption, and oedema, bronchospasm, hypotension

salt HR, our study confirms that ST should be performed as recommended by CEPO's (Comité de l'Évolution des Pratiques en Oncologie) recommendations.²⁹ A negative ST may predict with reasonable reliability the absence of future HR in case of reintroduction of drug infusion.²⁹ Because the IgE-mediated mechanism has never been demonstrated for pemetrexed, ST are not valid and have no diagnostic value for this molecule.

We recommend that patients who experience a HR onset should be monitored closely and clinicians must be aware of HR signs. Further exploration is needed to confirm ST utility in clinical practice.

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