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Etoposide hypersensitivity reactions and outcomes of desensitizations in immediate-type hypersensitivity reactions

Gözde Köycü Buhari[1], Sakine Nazik Bahçecioğlu[1], Selcan Gültuna[1], Özgür Akkale[1], Hatice Çelik Tuğlu[1], Onur Telli[1], Fatma Dindar Çelik[1], Melis Yağdıran[1], Dilek Çuhadar Erçelebi[1], Şenay Demir[1], Kurtuluş Aksu[1]

Department of Immunology and Allergy, Ankara Ataturk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

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ABSTRACT

Aims: This study aims to define characteristics of hypersensitivity reactions with etoposide, and outcomes of desensitizations in immediate-type hypersensitivity rections

Methods: This is a retrospective observational study of patients who had hypersensitivity reactions with etoposide from January 2019 to December 2023.

Results: A total of 39 patients with lung cancer were included in the study. Ten (25.6%) patients had known other drug allergies and three (7.7%) patients had previous chemotherapeutic hypersensitivity two with paclitaxel and one with docetaxel. Most of the initial hypersensitivities were in the first or second cycle (n=29, 74.4%). Ten (25.4%) patients had hypersensitivity reactions at the first application of etoposide. Thirty (76.9%) patients had immediate-type hypersensitivity reactions. There was no significant difference in terms of patient and initial hypersensitivity characteristics between patients who had immediate or non-immediate type hypersensitivity reactions. Of the 30 patients with immediate-type hypersensitivity reactions, initial reaction was mild in 16 (53.3%) and moderate in 14 (46.7%) patients. Most common symptoms were erythema in 29 (96.7%), dyspnea in 13 (43.3%), chest tightness in 8 (26.7%), discomfortness in 7 (23.3%), and hypertension in 6 (20%). Skin tests were negative in five patients who underwent skin testing. A total of 98 desensitization courses were performed in 27 patients and 3 (11.1%) patients had breakthrough reactions.

Conclusion: Most of the hypersensitivity reactions to etoposide are immediate-type and not severe. Desensitization is an effective and safe procedure to manage these reactions. Further research is needed to elucidate the mechanisms of hypersensitivity reactions.

Keywords: Etoposide, hypersensitivity, desensitization, reaction, immediate, chemotherapy

INTRODUCTION

Hypersensitivity reactions (HSRs) to chemotherapeutic agents and their management are important in clinical practice because they can not be easily replaced or exchanged to an alternative agent, and also alternative regimens may be less effective, more toxic, or more expensive than first-line chemotherapeutics.[1]

Etoposide is a semisynthetic derivative of epipodophylotoxin, which is effective against several types of malignancies, including lung cancer.[2] HSRs to etoposide are uncommon; the incidence is estimated to be between 1% and 3%.[3,4] The clinical presentations can vary from mild cutaneous to severe life-threatening reactions.[4-6]

Mild reactions may be prevented by premedication with corticosteroids and antihistamines or by prolonging the infusion time in some patients.[7] There are also reported cases of etoposide hypersensitivity managed by switching etoposide to etoposide phosphate.[8,9] However, patients who could not tolerate these methods were also reported.[10,11]

HSRs limit the use of chemotherapeutic agents because of their potential to cause more severe reactions or even death in the next administration.[12,13] In immediate-type HSRs, rapid drug desensitization can provide tolerance and reuse of the offending agent, thus giving patients a chance to be treated with first-line chemotherapeutics.[14] Although chemotherapeutic desensitization has been shown to be safe and effective, sometimes breakthrough reactions (BTRs) can be encountered during the procedure.[15]

Corresponding Author: Gözde KÖYCÜ BUHARİ, gozdekoycu@gmail.com

Data about etoposide HSRs is limited. This study aims to define characteristics of HSRs with etoposide, and outcomes of desensitizations in immediate-type HSRs.

METHODS

This is a retrospective observational study of patients who had HSRs with etoposide from January 2019 to December 2023 and were referred to our allergy and clinical immunology clinics. The study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Date: 27.12.2023, Decision No: 2012-KAEK-15/2863). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion criterias were patients who had symptoms compatible with HSR to etoposide and older than 18 years old. Exclusion criterias were insufficient medical records.

Baseline data including patients' characteristics (age, gender, diagnosis, comorbid diseases, previous drug allergy), treatment characteristics (therapy line, cycle number, day number of cycle), initial HSR characteristics (chronology, symptoms, severity), skin test results if performed, number of desensitization courses, occurrence of BTR, BTR characteristics (chronology, symptoms, severity) collected from medical records.

Chronologically, HSRs were classified as immediate and non-immediate reactions. Reactions that occurred during etoposide infusion or within 6 hours after the end of the infusion are classified as immediate-type hypersensitivity reactions. Reactions occurring more than 6 hours after the end of infusion are classified as non-immediate type HSRs.[16]

The severity of initial HSRs and BTRs were classified according to Brown's classification. The reaction was considered as mild if there was only cutaneous involvement, as moderate if there were symptoms suggesting respiratory, cardiovascular or gastrointestinal involvement and as severe if hypoxia, hypotension or neurologic compromise were considered.[17]

Skin tests with etoposide were conducted as follows: for the positive control, a prick test with a solution of histamine hydrochloride (10 mg/ml), whereas for the negative control, a physiological saline (0.9% saline) solution was used. A skin prick test was performed with a concentration of 20 mg/ml etoposide. After a negative skin prick result, an intradermal test was performed with a concentration of 0.2 mg/ml and 2 mg/ml etoposide. The prick test result was considered positive when the cutaneous response was a wheal of at least 3 mm with a surrounding flare, whereas the intradermal test result was considered positive with a wheal of at least 5 mm with a surrounding flare.

A 3-bag 12-step desensitization protocol described by Brigham and Women's Hospital was implemented 18. Written informed consent was obtained before each desensitization procedure. Thirty minutes before starting the desensitization, premedication with methylprednisolone 40 mg, H1- antihistamine (pheniramine 45,5 mg) and H2-antihistamine (famotidine 20 mg or ranitidine 50 mg) was administered as a routine practice of the oncology team before chemotherapy course. All desensitizations were carried under close observation with one-on-one nurse-to-patient care in the allergy unit. If any BTR occured during the protocol, infusion was suspended and the reaction was treated.

Statistical Analysis

All statistical analyses were performed using the SPSS (Statistical Package of Social Sciences) for Windows 18.0 software package. In evaluating the data, mean and standard deviation for normally distributed data, the median and interquartile range for data that did not show normal distribution, values, and percentages for ratios were determined by descriptive statistical method. In univariate analyses, Chi-square, Fisher, Student's t-test, and Mann-Whitney U tests were used, as appropriate. All p-values lower than 0.05 were considered to be statistically significant.

RESULTS

Patient Characteristics

A total of 39 patients, 35 (89.7%) male and 4 (10.3%) female with mean age 59.08±7.8 (range 47-76) were included in the study. The pathological diagnosis was small cell lung cancer (SCLC) in 30 (76.9%), non-small cell lung cancer (NSCLC) in 6 (15.4%) and combined small and non-small cell lung cancer in 3 (7.7%) patients. Metastatic disease was present in 20 (51.3%) patients.

Systemic comorbidities were present in 19 (48.7%) patients; 12 (30.8%) had hypertension, 5 (12.8%) had coronary arterial disease, 4 (10.3%) had diabetes mellitus, and each one patient (2.6%) had hyperlipidemia, hypothyroidism and chronic hepatitis B virus infection. Fifteen (64.1%) of the patients were receiving chronic obstructive pulmonary disease treatment. Median smoking duration was 40 (25-110) pack years in 19 patients for whom smoking information was available.

Ten (25.6%) patients had known other drug allergies; four had beta-lactam, two had paclitaxel, one had docetaxel, one had radiocontrast media, one had lansoprazole allergy, and another patient had a history of multi-drug allergy to nonsteroidal anti-inflammatory drugs, beta-lactam antibiotics, and fentanyl.

Treatment and Initial HSR Characteristics

The initial HSR was observed in 36 (92.3%) patients during the first-line therapy and 3 (7.7%) patients during the second-line therapy. Of the three patients who received second-line treatment, two developed a reaction in the first cycle, and one in the second cycle.

In evaluating all patients the initial HSR was observed in most patients in the first or second cycle with a median value of 2 (range 1-8). It was in the first cycle in 18 (46.15%) patients, second cycle in 11 (28.20%), third cycle in 3 (7.69%), fourth cycle in one (2.56%), fifth cycle in 3 (7.69%) and sixth, seventh and eight cycle in each one (2.56%) patient. Ten (25.4%) patients had HSR at the first application of etoposide.

In evaluating the day of the cycle that the reaction developed, it was on the first day in 23 (59.0 %) patients, on the second day in 14 (35.9%) patients, and on the third day in 2 (5.1%) patients.

According to the reaction chronology, 30 (76.9%) patients had immediate-type HSRs. Twenty-five (83.3%) of these reactions occurred during etoposide infusion, and 20 (66.6%) of them were during the first half of the infusion. Five (20%) of the immediate-type HSRs occurred within the first hour after infusion. Nine (23.1%) patients had non-immediate type HSRs, which were developed at least 6 hours after the etoposide infusion.

Of the 30 patients with immediate-type HSR, initial HSR was mild in 16 (53.3%) and moderate in 14 (46.7%) patients. Most common symptoms were erythema in 29 (96.7%), dyspnea in 13 (43.3%), chest tightness in 8 (26.7%), discomfortness in 7 (23.3%), and hypertension in 6 (20%). All patients with non-immediate type HSR had mild reactions with erythema in all 9 (100%) patients and also angioedema in 3 (33.3%) cases. Clinical symptoms of the HSRs are shown in **Table 1**.

Table 1. Clinical symptoms of hypersensitivity reactions

Clinical symptoms	Immediate-type HSR n=30	Non-immediate type HSR n=9
Erythema n (%)	29 (96.7)	9 (100)
Dyspnea n (%)	13 (43.3)	-
Chest tightness n (%)	8 (26.7)	-
Discomfortness n (%)	7 (23.3)	-
Hypertension n (%)	6 (20)	-
Angioedema n (%)	4 (13.3)	3 (33.3)
Warmth n (%)	4 (13.3)	-
Sweating n (%)	3 (10)	-
Back pain n (%)	2 (6.7)	-
Abdominal pain n (%)	1 (3.3)	-

HSR: Hypersensitivity reaction

There was no significant difference in terms of patient and initial hypersensitivity characteristics between patients who had immediate or non-immediate type HSRs (**Table 2**).

Table 2. Patient and initial hypersensitivity reaction characteristics

	All patients n=39	Patients with Immediate-type HSR n=30	Patients with non-immediate type HSR n=9	p
Age (mean±SD)	59.08±7.8	58±7.65	56±8.61	0.973
Sex n (%)				
Female	4 (10.3)	3 (10)	1 (11.1)	1.000
Male	35 (89.7)	27 (90)	8 (88.9)	
Diagnosis n (%)				
SCLC	30 (76.9)	23 (76.7)	7 (77.8)	0.886
NSCLC	6 (15.4)	5 (16.7)	1 (11.1)	
Combined	3 (7.7)	2 (6.7)	1 (11.1)	
Metastatic disease n (%)	20 (51.3)	18 (60)	2 (22.2)	0.065
Systemic comorbidity n (%)	19 (48.7)	17 (56.7)	2 (22.2)	0.127
Drug allergy n (%)	10 (25.6)	7 (23.3)	3 (33.3)	0.669
Therapy lines n (%)				
First line	36 (92.3)	27 (90)	9 (100)	
Second line	3 (7.7)	3 (10)	-	
Cycle number n (%)				
1st	19 (48.7)	12 (40.0)	7 (77.8)	
2nd	10 (25.6)	8 (26.7)	2 (22.2)	
≥3rd	10 (25.6)	10 (33.3)	-	
Total cycle number, median (min-max)	2 (1-8)	2 (1-8)	1 (1-2)	0.070
Day of reaction on the cycle n (%)				
1st day	23 (59.0)	16 (53.3)	7 (77.8)	
2nd day	14 (35.9)	12 (40.0)	2 (22.2)	
3rd day	2 (5.1)	2 (6.7)	-	
Day of reaction on the cycle, median (min-max)	1 (1-3)	1 (1-3)	1 (1-2)	0.178

HSR: Hypersensitivity reaction, NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer

Management of Immediate-type HSRs and Outcomes of Desensitizations

Skin prick and intradermal tests with etoposide were performed on five patients with immediate-type HSRs; all were negative.

Re-administration of etoposide with a slow infusion rate was tried in 2 patients with mild reactions but was not successful.

Etoposide was discontinued in 3 patients after hypersensitivity reactions. In the remaining 27 patients, etoposide was given with desensitizations. A total of 98 desensitization courses were performed during the study period. The median number of desensitization courses was 2 (range 1-12).

A total of 3 BTRs developed in three (11.1%) patients. Two of these patients had mild initial reactions; after desensitizations, they had erythematous cutaneous reactions in the late period (≥6 hours,; one after the first desensitization and the other after the second desensitization course. The third patient with a moderate initial reaction had a mild breakthrough reaction in the last step of the first desensitization course. The procedure was interrupted, and the reaction was treated, but the patient subsequently refused to continue the procedure.

DISCUSSION

In this study, we retrospectively reported the characteristics of initial HSRs with etoposide and the outcomes of desensitizations in patients with immediate-type hypersensitivity. We found that most of the reactions were immediate-type HSRs. There was no significant difference in terms of patient and initial hypersensitivity characteristics between patients with immediate or non-immediate type HSRs.

The most common symptoms of immediate-type HSRs were erythema, dyspnea, and chest tightness. Similarly, previous studies have reported dyspnea, erythema, flushing, angioedema, throat tightness, chest pain or tightness, wheezing, cough, and cyanosis as the most common symptoms.[4,19,20]

The exact mechanism of etoposide HSRs are not fully known. The fact that most of the reactions in our study were observed during the first and second cycle, and even in 25.4% of the patients during the first application, and no skin test positivity was detected in any of the patients tested, suggests that these reactions may not be IgE-mediated.

HSRs to etoposide were assumed to be secondary to its diluent polysorbate 80.[9] Polysorbate 80 consists of a mixture of fatty acid esters of sorbitol-derived cyclic ethers and polyethylene glycol. It induces immediate-type non-IgE-mediated hypersensitivity reactions via complement activation and basophile degranulation.[10]

Polysorbate 80 is also used as a solubilizing agent in the docetaxel formulation.[21] The fact that one of the patients in our study had previous docetaxel hypersensitivity suggests that polysorbate 80 may be the responsible component in this patient. In our study, two patients also had a history of paclitaxel hypersensitivity. Although a different solubilizer, cremophor EL, is used in the paclitaxel formulation Friedland et al. reported possible cross-reaction between paclitaxel and etoposide.[21,22] Caution should be exercised against etoposide hypersensitivity in patients with a history of hypersensitivity to taxanes.

Etoposide phosphate is a water-soluble prodrug of etoposide that does not contain polysorbate 80 but contains dextran 40.[23] There are previous reports of patients who had HSR with etoposide but tolerated etoposide phosphate.[9,24] There are also reports of patients who tolerated etoposide after a hypersensitivity reaction to etoposide phosphate.[5,23]

However, there are reported cases of hypersensitivity to both etoposide and etoposide phosphate, suggesting that HSRs may not be related to diluents but to etoposide itself.[10,25] Although they are not standardized, there are also reports of skin test positivity in patients with etoposide hypersensitivity, suggesting an IgE-mediated mechanism.[26,27] Skin testing protocols with etoposide should be standardized with further studies.

In our study, patients with immediate-type HSRs to etoposide had mild to moderate reactions; however, severe or life-threatening reactions have been reported previously.[4,19]

If an HSR occurs with chemotherapeutics, the physician must decide whether to continue treatment or not. Re-administration of the culprit drug carries the risk of a potentially fatal anaphylactic reaction; however, changing to an alternative drug can have a negative effect on patients' outcomes.[1]

Etoposide hypersensitivity was found to be associated with higher infusion rates and may be prevented by slow infusion.[19] In our study, re-administration of etoposide with slow infusion was tried in 2 patients with mild reactions; however, it was unsuccessfull. Another management option is challanging etoposide with a prophylactic regimen containing corticosteroids and antihistamines.[7,28] Hudson et al.[7] reported 78% of patients were rechallenged successfully to intravenous etoposide.

Desensitization, which allows temporary tolerance to a drug, is another option to continue the therapy.

Several etoposide desensitization protocols have been reported in the literature.[4,29,30] We used a 3-bag 12-step desensitization protocol described by Brigham and Women's Hospital 18. During the study period, a total of 98 desensitizations were performed in 27 patients with immediate-type HSRs and only three BTRs were observed in three (11.1%) patients. All of the BTRs were mild graded; two of them were developed in the late period (≥6 hours) after desensitization. These results suggest that desensitization is an effective and safe method in managing patients with etoposide HSRs.

Limitations

However this study has some limitations. First limitation was the retrospective design of the study. Second limitation was slow infusion or premedication escalation was not attempted in all patients with mild reactions. Drug tolerance could not be achieved in two cases in which slow infusion was attempted. In our hospital, 12 mg dexamethasone is given in routine practice before an etoposide cure, and no increase in premedication has been tried in patients.

CONCLUSION

Most of the hypersensitivity reactions to etoposide are immediate-type and not severe; however, the mechanism is not clear. Further research is needed to elucidate the mechanisms. Desensitization is an effective and safe procedure to manage these reactions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Date: 27.12.2023, Decision No: 2012-KAEK-15/2863).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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