

Clinical Communications

Successful rapid desensitization to intravenous etoposide using a 14-step protocol

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Clinical Implications

- We report the success of a rapid desensitization protocol for intravenous etoposide on a woman with limited-stage small cell lung carcinoma. A variation of a 12-step drug desensitization protocol was used.

TO THE EDITOR:

Chemotherapeutic agents used for treating neoplastic disease have the potential to induce hypersensitivity reactions (HSRs). With an increase in the use of these drugs, the potential for HSRs has also increased and more cases are frequently being reported. According to Cernadas et al,¹ drug hypersensitivity accounts for more than 15% of all adverse drug reactions, affecting more than 7% of the general population and 10% to 20% of all hospitalized patients. Because these reactions often require the discontinuation of first-line therapies to avoid a life-threatening situation, oncologists have been increasingly consulting allergists to assist in the management of these HSRs.¹⁻⁶

Available options to solve the problem in the presence of HSRs include changing drugs, premedicating with antihistamines and corticosteroids, and/or desensitization. Unfortunately, prescribing an alternative medication is not always feasible especially in the case of targeted therapies, which demand the use of a specific drug. Although a premedication treatment can diminish or prevent the risk of HSRs, it is not sufficient by itself because these drugs often only mask early signs of HSRs rather than prevent them.^{1-3,6-8}

Etoposide, an antimitotic epipodophyllotoxin active against numerous malignant conditions including germ cell neoplasms, lymphomas, and carcinomas is reported to induce HSRs in 6% of the patients. However, its incidence of anaphylaxis is 0.7%.² Manifestations of HSRs to etoposide vary but tend to include bronchospasms, dyspnea, and hypotension.¹⁻³

Multiple desensitization studies and case reports have suggested that HSRs to chemotherapeutic agents can be avoided with low infusion rates and managed with the use of pre-treatments that include antihistamines and corticosteroids.^{2,8,9}

We present a case in which a 79-year-old woman with limited-stage small cell lung carcinoma was admitted to Mercy Hospital and Medical Center in Chicago for oncology treatment. As she was receiving her second cycle of intravenous etoposide, she developed an anaphylactic reaction. Five minutes into the etoposide infusion, the patient immediately became dyspneic, tachypneic, tachycardic, and hypotensive, developed generalized pruritus with dermatographia, and had oxygen desaturation. She described feeling a sensation she would refer as “taking me out of the world,” notified the nurse, and the treatment was stopped. Given the instantaneous onset of HSR manifestations, it was concluded that etoposide was

TABLE I. Prepared solutions

Solution	Dose in each solution (mg)*	Volume (mL)	Solution concentration (mg/mL)
A	0.4125	250	0.00165
B	4.125	250	0.0165
C	165	1000	0.165

*The sum of the doses in the 3 solutions is 169.538 mg. Because solutions A and B were partially administered, the total dose infused is 165.1679 mg.

responsible because no other chemotherapeutic was being administered. Six days later, she was admitted to the hospital for desensitization to etoposide by the immunology service because etoposide was the most suitable chemotherapeutic option for her condition given the drug's unique mechanism of action.

Castells et al⁶ developed a standard 12-step rapid drug desensitization (RDD) protocol that involves the infusion of the target dose in 12 incremental steps over a multiple-hour time span. Following the 12-step RDD protocol, we decided to implement the procedure with slight variations; given the patient's poor performance status, 2 additional steps were added to administer the dose over a longer time span, giving a total of 14 steps. A premedication treatment was given before desensitization to diminish the risk of breakthrough reactions. This included the following:

- Diphenhydramine (50 mg ivp)
- Zofran (24 mg ivpb)
- Epinephrine (1 mg ivp)
- Heparin (500 units flush)
- Dexamethasone (10 mg)

Via 3 solutions, the target dose of 165 mg was then administered over the span of 15.75 hours in 14 consecutive steps at increasing infusion rates (Table I). The volume of bag C was 4 times that of bags A and B (1000, 250, and 250 mL of D5W, respectively) to increase the infusion time span. The solutions followed a 10-fold serial dilution. Each step took 15 minutes, and the dose was increased by 2 to 2.5-fold (Table II).

The patient received the target dose with no complications or breakthrough reactions. The 14-step RDD protocol was effective in treating the patient's hypersensitivity to etoposide. Using the same 14-step protocol, 2 additional cycles of chemotherapy were administered and induced no further HSRs. However, the patient showed poor performance to the regimen after the fourth cycle and was switched to a different drug combination.

RDD has been a widely used method that provides temporary drug tolerance.¹⁻⁸ The stepwise method of drug administration called for by the standard protocol reduces the chances or severity of HSRs because of the slow and highly controlled infusion process. Castells et al have demonstrated *in vitro* that rapid desensitization inhibits the mechanisms responsible for inducing antigen-specific mast cell degranulation.^{3,6} On the basis of these findings, Castells and the Brigham and Women's Hospital Desensitization Program developed a 12-step RDD protocol that has proven the validity of these discoveries; the Brigham and Women's Hospital Desensitization Protocol has effectively desensitized 99.9% of nearly 800 patients to various drugs.^{3,6}

TABLE II. 14-Step desensitization protocol [Refs. 1,3,4,6-9]*

Step	Solution	Rate (mL/h)	Time (h)	Administered dose (mg)	Cumulative dose (mg)	Volume infused (mL)
1	A	2	0.25	0.000825	0.000825	0.5
2	A	5	0.25	0.0020625	0.002888	1.25
3	A	10	0.25	0.004125	0.007013	2.5
4	A	20	0.25	0.00825	0.015263	5
5	B	2	0.25	0.00825	0.023513	0.5
6	B	5	0.25	0.020625	0.044138	1.25
7	B	10	0.25	0.04125	0.085388	2.5
8	B	20	0.25	0.0825	0.167888	5
9	C	2	0.25	0.0825	0.250388	0.5
10	C	5	0.25	0.20625	0.456638	1.25
11	C	10	0.25	0.4125	0.869138	2.5
12	C	20	0.25	0.825	1.694138	5
13	C	40	0.25	1.65	3.344138	10
14	C	80	12.5	161.8238	165.1679	980.75

*A target dose of 165.1679 mg was infused in 1018.50 cc of solution over 15.75 h.

Álvarez Cardona et al⁹ describe a similar case report in which the 12-step RDD protocol was implemented with success on a patient who experienced an HSR to etoposide. However, despite the remarkable efficacy of the 12-step RDD protocol, there are no individual case reports in the English medical literature of desensitization to intravenous etoposide. Given the success of the modified, 14-step protocol in our patient, we find it pertinent to communicate our experience.

The management of HSRs needs to be continually refined, and known treatment methods need to be disseminated. Depending on their performance status, patients experiencing HSRs to etoposide who are without drug alternatives may find either the 12-step or the 14-step RDD protocol an effective treatment option. Further case reports ought to be published and studies conducted to support this conclusion.

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Conflict of interest: The authors declare that they have no relevant conflicts of interest.

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