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Title: A case-series of pediatric oncology patients undergoing successful rapid etoposide desensitization

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To the Editor:

Etoposide is a podophyllotoxin used in the treatment of various pediatric neoplasms. Hypersensitivity reactions (HSR) to etoposide have a reported incidence of about 1-3%, with symptoms ranging from mild cutaneous reactions to fatal anaphylaxis.¹⁻² HSR to etoposide are thought to be related to the vehicle used to dissolve etoposide, polysorbate 80, rather than the drug.³ In an animal model, polysorbate 80 has been shown to cause HSR, given its histamine-releasing properties.⁴ Patients experiencing HSR to etoposide may have their treatment substituted with etoposide phosphate, a water-soluble prodrug of etoposide which does not contain polysorbate 80. In August 2016, etoposide phosphate went on national backorder, limiting therapeutic options for patients who experienced a clinically significant hypersensitivity reaction to etoposide. Rapid drug desensitization allows temporary tolerance to a drug in order for a medication-allergic patient to receive the optimal agent based on their clinical condition and offers an option for patients in need of etoposide who have had an HSR.⁵ Drug desensitization protocols have been successfully reported with a variety of chemotherapeutic agents, including etoposide. However, the majority of reported protocols were designed for adult patients.⁵⁻⁸ We describe the development and successful implementation of both a 13-step and 15-step rapid drug desensitization protocol for etoposide in a cohort of pediatric oncology patients.

Between December 2016 and September 2017, during the national etoposide phosphate shortage, a total of 75 patients received etoposide in our institution. Nine out of the 75 patients had a documented etoposide hypersensitivity reaction and underwent 22 cycles of desensitization to etoposide. Median patient age was 6 years (IQR 4.5 - 16.0) and 55.6% of patients were female. The most common malignancy was neuroblastoma (55.6%; n=5), followed by Hodgkin lymphoma (22.2%; n=2), Wilms tumor (11.1%; n=1), and germ cell tumor (11.1%; n=1). The hypersensitivity reactions were graded based on the World Allergy Organization (WAO) Anaphylaxis Grading criteria.⁹ Six (67%) patients experienced a Grade 2 hypersensitivity reaction, while 1 (11%) patient had a Grade 3 and 2 (22%) patients experienced a Grade 4 reaction at the time of their reaction. Respiratory symptoms were observed in all patients experiencing a reaction, including but not limited to shortness of breath, coughing, wheezing and/or oxygen desaturations. Seven patient reported cutaneous findings, including hives, erythema of the skin, lip swelling and/or itching. Cardiovascular symptoms, manifested as hypotension, were noted in only 2 patients. Four patients experienced perioral cyanosis with an oxygen desaturation below 90 percent. Generally, drug allergy skin testing is done in order to confirm whether reactions were due to an IgE-mediated process. In all nine patients, drug allergy testing to etoposide could not be performed given the immediate need to treat each patient's oncologic condition.

Based on previous publications,⁵⁻⁸ we initially implemented a modified 13-step rapid drug desensitization protocol (Table I). However, due to concentration-dependent stability of etoposide, which may precipitate at concentrations greater than 0.4 mg/mL, and volume restrictions in the pediatric population, we subsequently developed five different dose-based desensitization protocols. Therefore, the development of dose-based and dilution-based desensitization protocols were key in our pediatric oncology population. These protocols were developed and divided into the following etoposide treatment doses: 1) less than 40 mg; 2) 41 - 90 mg; 3) 91 - 200 mg; 4) 201 - 240 mg; and 5) 241 mg - 300 mg (see Table E1-E5 in the Online Repository for dose-based calculations for each 13-step desensitization protocol). Each protocol consisted of a 3-bag solution system, with a ten-fold increase in concentration from bag 1 to bag 3. All etoposide desensitizations were conducted in the pediatric intensive care unit (PICU). Intervals between cycles of chemotherapy administration were

generally 3 to 4 weeks, as dictated by the patient's respective oncology treatment protocol. The aforementioned desensitization process was repeated on Day 1 for each of the subsequent cycles.

In order to reduce the potential nonimmunologic/histaminergic effects caused by etoposide, we chose to premedicate our patients with antihistamines one day prior to the infusion, in order to provide them the best opportunity to receive etoposide without any adverse events. Twenty-four hours prior to initiating etoposide desensitization, all patients received a standardized protocol of premedication with cetirizine (10 mg, administered orally once daily) and ranitidine (3 mg/kg, maximum dose: 150 mg, administered orally every 12 hours). Patients were also premedicated 30 minutes prior to initiating the desensitization protocol with diphenhydramine (1 mg/kg, maximum dose: 50 mg, administered intravenously), ranitidine (3 mg/kg, maximum dose: 150 mg, administered orally), and hydrocortisone (2 mg/kg, maximum dose: 200 mg, administered intravenously). Following a successful multi-step desensitization on Day 1, subsequent doses of etoposide within the treatment cycle were administered as a single-dose within 24-48hrs of the previous dose. These were administered at half the standard rate following repeat premedication.

Eight of nine patients (89%) successfully tolerated the 13-step desensitization protocol. One patient reported throat tightness at 45 minutes into the initial desensitization (Bag 1, Step 3 - 0.875 mL = 0.003 mg administered). The infusion was discontinued with symptoms resolving immediately without any further pharmacologic intervention. The patient was subsequently treated with a 15-step desensitization protocol (Table II), which was well-tolerated during the subsequent 2 chemotherapy cycles.

This is the first case series to focus on etoposide desensitization in a cohort of pediatric oncology patients. Given the urgency for treatment and the shortage of the water-soluble pro-drug of etoposide, etoposide phosphate, confirmatory skin testing for etoposide was not an option at the time, therefore our multi-disciplinary team successfully developed a 13-step and 15-step etoposide desensitization protocol to safely provide etoposide per the individual's oncology treatment protocol. Here we highlight the uniqueness of pediatric oncology patient management, which makes a singular desensitization protocol challenging. In the setting of a national shortage of etoposide phosphate, we report a standardized 13- and 15-step etoposide desensitization protocol that is both safe and effective

in the treatment of pediatric oncology patients who have experienced hypersensitivity reactions to etoposide.

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vi. Author contributions

TEW: made substantial contribution to conception and design of protocols, acquisition of data, substantial drafting of the manuscript, and provided final approval of this version to be published

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viii. TABLES

Table I: A 13-step pediatric desensitization protocol to etoposide (based on a target dose of 138 mg)

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.5	0.00138	0.00138
2	1	5	15	1.25	0.00345	0.00483
3	1	10	15	2.5	0.0069	0.01173
4	1	20	15	5	0.0138	0.02553
5	2	5	15	1.25	0.0345	0.06003
6	2	10	15	2.5	0.069	0.12903
7	2	20	15	5	0.138	0.19803
8	2	40	15	10	0.276	0.47403
9	3	10	15	2.5	0.69	1.16403
10	3	20	15	5	1.38	2.54403
11	3	40	15	10	2.76	5.30403
12	3	80	15	20	5.52	10.82403
13	3	115	240	460.5	127.1	138

Solution 1*: volume 250 mL, concentration 0.00276 mg/mL, total dose in solution 0.69 mg

Solution 2*: volume 250 mL, concentration 0.0276mg/mL, total dose in solution 6.9mg

Solution 3: volume 500 mL, concentration 0.276 mg/mL, total dose in solution 138 mg

*Solutions 1 and 2 were partially infused

Total duration = 7 hours

Table II: A 15-step pediatric desensitization protocol to etoposide (based on target dose of 268 mg)

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	0.5	15	0.125	0.00043	0.00043
2	1	1	15	0.25	0.00085	0.00128
3	1	2	15	0.5	0.0017	0.003
4	1	5	15	1.25	0.00425	0.0073
5	2	2	15	0.50	0.017	0.024
6	2	5	15	1.25	0.043	0.067
7	2	10	15	2.50	0.085	0.152
8	2	20	15	5.00	0.17	0.32
9	2	40	15	10.00	0.3	0.66
10	3	5	15	1.25	0.425	1.1
11	3	10	15	2.50	0.85	1.95
12	3	20	15	5.00	1.7	3.65
13	3	40	15	10.00	3.4	7.1
14	3	80	15	20.00	6.8	13.9
15	3	115	379	726	254.1	268

Solution 1*: volume 250 mL, concentration 0.0034 mg/mL, total dose in solution 0.85 mg

Solution 2*: volume 250 mL, concentration 0.034mg/mL, total dose in solution 8.5mg

Solution 3: volume 800 mL, concentration 0.34 mg/mL, total dose in solution 272 mg

*Solutions 1 and 2 were partially infused

Total duration = 9.8 hours

ix. APPENDICES

Table E1: Dose-based calculations for etoposide doses less than 40mg and 13-step protocol

Table E2: Dose-based calculations for etoposide doses 41-90mg and 13-step protocol

Table E3: Dose-based calculations for etoposide doses 91-200mg and 13-step protocol

Table E4: Dose-based calculations for etoposide doses 201-240mg and 13-step protocol

Table E5: Dose-based calculations for etoposide doses 241-300mg and 13-step protocol

1 Table S1: Dose-based calculations for etoposide doses less than 40mg

Solution	Volume (mL)	Concentration (mg/mL)	Total amount of drug in each solution (mg)
Solution 3	100	(A)	(D)
Solution 2	60 mL	(B)	(E)
Solution 1	60 mL	(C)	(F)

- 2
- 3 **Step A:** Total dose of etoposide $\div$ 100 mL (must be <0.4 mg/mL) = concentration of solution 3
- 4 **Step B:** Concentration of solution 3 $\div$ 10 = concentration of solution 2
- 5 **Step C:** Concentration of solution 3 $\div$ 100 = concentration of solution 1
- 6 **Step D:** Concentration of solution 3 $\times$ 100 mL = total amount of drug in solution 3
- 7 • Note: this should equal the full dose of etoposide for this patient
- 8 **Step E:** Concentration of solution 2 $\times$ 60 mL = total amount of drug in solution 2
- 9 **Step F:** Concentration of solution 1 $\times$ 60 mL = total amount of drug in solution 1

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	1	15	0.25		
2	1	2.5	15	0.625		
3	1	5	15	1.25		
4	1	10	15	2.5		
5	2	2.5	15	0.625		
6	2	5	15	1.25		
7	2	10	15	2.5		
8	2	20	15	5		
9	3	5	15	1.25		
10	3	10	15	2.5		
11	3	20	15	5		
12	3	40	15	10		
13	3	60	80.2	80.2		

10 Total duration = 4.3 hours

1 Table S2: Dose-based calculations for etoposide doses 41-90mg

Solution	Volume (mL)	Concentration (mg/mL)	Total amount of drug in each solution (mg)
Solution 3	250 mL	(A)	(D)
Solution 2	150 mL	(B)	(E)
Solution 1	150 mL	(C)	(F)

2

3 **Step A:** Total dose of etoposide $\div$ 250 mL (must be <0.4 mg/mL) = concentration of solution 3

4 **Step B:** Concentration of solution 3 $\div$ 10 = concentration of solution 2

5 **Step C:** Concentration of solution 3 $\div$ 100 = concentration of solution 1

6 **Step D:** Concentration of solution 3 $\times$ 250 mL = total amount of drug in solution 3

7 • Note: this should equal the full dose of etoposide for this patient

8 **Step E:** Concentration of solution 2 $\times$ 150 mL = total amount of drug in solution 2

9 **Step F:** Concentration of solution 1 $\times$ 150 mL = total amount of drug in solution 1

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.5		
2	1	5	15	1.25		
3	1	10	15	2.5		
4	1	20	15	5		
5	2	5	15	1.25		
6	2	10	15	2.5		
7	2	20	15	5		
8	2	40	15	10		
9	3	10	15	2.5		
10	3	20	15	5		
11	3	40	15	10		
12	3	80	15	20		
13	3	100	126	210.5		

10

1 Table S3: Dose-based calculations for etoposide doses 91-200mg

Solution	Volume (mL)	Concentration (mg/mL)	Total amount of drug in each solution (mg)
Solution 3	500 mL	(A)	(D)
Solution 2	250 mL	(B)	(E)
Solution 1	250 mL	(C)	(F)

2

3 **Step A:** Total dose of etoposide $\div$ 500 mL (must be <0.4 mg/mL) = concentration of solution 3

4 **Step B:** Concentration of solution 3 $\div$ 10 = concentration of solution 2

5 **Step C:** Concentration of solution 3 $\div$ 100 = concentration of solution 1

6 **Step D:** Concentration of solution 3 $\times$ 500 mL = total amount of drug in solution 3

7 • Note: this should equal the full dose of etoposide for this patient

8 **Step E:** Concentration of solution 2 $\times$ 250 mL = total amount of drug in solution 2

9 **Step F:** Concentration of solution 1 $\times$ 250 mL = total amount of drug in solution 1

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50		
2	1	5.0	15	1.25		
3	1	10.0	15	2.50		
4	1	20.0	15	5.00		
5	2	5.0	15	1.25		
6	2	10.0	15	2.50		
7	2	20.0	15	5.00		
8	2	40.0	15	10.00		
9	3	10.0	15	2.50		
10	3	20.0	15	5.00		
11	3	40.0	15	10.00		
12	3	80.0	15	20.00		
13	3	115.0	240	460.5		

10

1 Table S4: Dose-based calculations for etoposide doses 201-240mg

Solution	Volume (mL)	Concentration (mg/mL)	Total amount of drug in each solution (mg)
Solution 3	600 mL	(A)	(D)
Solution 2	250 mL	(B)	(E)
Solution 1	250 mL	(C)	(F)

2

3 **Step A:** Total dose of etoposide $\div$ 600 mL (must be <0.4 mg/mL) = concentration of solution 3

4 **Step B:** Concentration of solution 3 $\div$ 10 = concentration of solution 2

5 **Step C:** Concentration of solution 3 $\div$ 100 = concentration of solution 1

6 **Step D:** Concentration of solution 3 $\times$ 600 mL = total amount of drug in solution 3

7 • Note: this should equal the full dose of etoposide for this patient

8 **Step E:** Concentration of solution 2 $\times$ 250 mL = total amount of drug in solution 2

9 **Step F:** Concentration of solution 1 $\times$ 250 mL = total amount of drug in solution 1

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50		
2	1	5.0	15	1.25		
3	1	10.0	15	2.50		
4	1	20.0	15	5.00		
5	2	5.0	15	1.25		
6	2	10.0	15	2.50		
7	2	20.0	15	5.00		
8	2	40.0	15	10.00		
9	3	10.0	15	2.50		
10	3	20.0	15	5.00		
11	3	40.0	15	10.00		
12	3	80.0	15	20.00		
13	3	115.0	288	560		

10

1 Table S5: Dose-based calculations for etoposide doses 241-300mg

Solution	Volume (mL)	Concentration (mg/mL)	Total amount of drug in each solution (mg)
Solution 3	800 mL	(A)	(D)
Solution 2	250 mL	(B)	(E)
Solution 1	250 mL	(C)	(F)

2

3 **Step A:** Total dose of etoposide ÷ 800 mL (must be <0.4 mg/mL) = concentration of solution 3

4 **Step B:** Concentration of solution 3 ÷ 10 = concentration of solution 2

5 **Step C:** Concentration of solution 3 ÷ 100 = concentration of solution 1

6 **Step D:** Concentration of solution 3 x 800 mL = total amount of drug in solution 3

7 • Note: this should equal the full dose of etoposide for this patient

8 **Step E:** Concentration of solution 2 x 250 mL = total amount of drug in solution 2

9 **Step F:** Concentration of solution 1 x 250 mL = total amount of drug in solution 1

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50		
2	1	5.0	15	1.25		
3	1	10.0	15	2.50		
4	1	20.0	15	5.00		
5	2	5.0	15	1.25		
6	2	10.0	15	2.50		
7	2	20.0	15	5.00		
8	2	40.0	15	10.00		
9	3	10.0	15	2.50		
10	3	20.0	15	5.00		
11	3	40.0	15	10.00		
12	3	80.0	15	20.00		
13	3	115.0	396	760		

10