

Successful desensitization protocol for delayed cutaneous eruption to temozolomide

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Clinical Implication

- A successful rapid desensitization to temozolomide using commercially available doses in an outpatient setting for a delayed cutaneous eruption.

TO THE EDITOR:

Classically, drug desensitization ameliorates immediate-type hypersensitivity reactions.¹ However, an increasing number of reports suggest that delayed-type reactions may respond to rapid desensitization.² Temozolomide is first-line therapy for high-grade glioma.³ Both immediate and delayed hypersensitivity reactions (HSR) to temozolomide occur.^{4,5} We describe a novel protocol, using commercially available doses, that permits outpatient desensitization for a delayed cutaneous eruption to temozolomide.

Our patient was a 26-year-old man with a history of right frontal lobe oligastrocytoma, World Health Organization grade II-III (Figure 1). He was started on temozolomide 325 mg daily for 5 days every 28 days. He tolerated the first 2 of 12 cycles without adverse reaction. However, on day 2 of cycle 3, he developed a diffuse rash with erythematous patches and macules over his torso, arms, legs, palms, and soles. The rash was pruritic and painful. There was no blistering, desquamation, angioedema, or mucosal involvement. There were no associated respiratory, cardiovascular, or gastrointestinal symptoms, or other signs of anaphylaxis. A clinical diagnosis of drug hypersensitivity to temozolomide was made by the neuro-oncologist who prescribed cessation of this therapy and a course of prednisone. The rash dramatically improved without interruption of his antiepileptic lacosamide.

He was referred to an Allergy-Immunology specialist for desensitization because temozolomide was the optimal treatment for his disease. At that time, a faint blanching, pink rash persisted, which later responded to topical steroids and sun avoidance. We agreed with the clinical diagnosis of delayed HSR to temozolomide. Skin prick testing and patch testing were not performed because the negative and positive predictive values of these tests with temozolomide are unknown. We had concerns about possible skin toxicity with either method for both the patient and potential volunteers to determine the nonirritating concentrations of this drug. A biopsy specimen was not obtained, thus the exact immunologic nature of the rash is unclear. However, the results of these investigations would not have changed management given our high index of suspicion for delayed HSR.² In a published report, the clinical diagnosis of hypersensitivity to temozolomide was confirmed by oral challenge, which precipitated a severe reaction.⁵ Drug challenge was declined given concern that recurrence of the rash would further delay therapy.

For chemotherapy cycles 4 to 8, the patient underwent 5 rapid desensitizations adapted from published protocols (Table 1).^{5,6}

Compounding temozolomide required inpatient pharmacy expertise and facilities for preparation and administration of the initial doses. Thus, he was admitted for medication formulation and monitoring. All the doses were taken at 30-minute intervals on an empty stomach to facilitate absorption. He was premedicated with prednisone 30 mg daily, cetirizine 10 mg daily, and famotidine 20 mg twice a day for days 1 to 5. Because the patient demonstrated no evidence of HSR on days 1 and 2, he was deemed very low risk for immediate hypersensitivity. He self-administered the protocol at home for days 3 to 5. He received an epinephrine autoinjector and counseling about the signs and symptoms of immediate HSR, including anaphylaxis. He experienced no recurrence of the rash or other adverse effects during this period.

Monthly inpatient desensitization protocols proved resource intensive and cumbersome for the patient. After advising him of the increased risk of reaction, we modified our protocol for cycles 9 to 12 to eliminate the need for hospitalization and complete the entire desensitization as an outpatient. Because our outpatient pharmacy could not supply custom-made serial dilutions, we started the ninth cycle of chemotherapy (sixth desensitization) at 5 mg, the lowest commercially available dose. Additional protocol changes included administering the initial dose on a full stomach and extending the intervals to 45 minutes between steps 1, 2, and 3. These modifications were designed to slow absorption, decrease bioavailability, and mimic the minute quantities administered during the initial phases of the inpatient protocol (Table 1). The goal dose was adjusted by the neuro-oncologist to 250 mg due to thrombocytopenia. The patient's premedications remained the same, except that the prednisone dose was decreased to 20 mg for desensitizations 7 to 9 to minimize steroid intolerance. This outpatient, "higher initial dose" desensitization protocol was well tolerated without recurrence of the rash or evidence of anaphylaxis.

On day 1 of the eighth desensitization, the patient experienced a brief seizure 30 minutes after receiving the first dose of temozolomide, without signs or symptoms of immediate hypersensitivity. The neuro-oncologist agreed with our assessment that this was a breakthrough seizure, not a drug reaction. Magnetic resonance imaging performed shortly after the seizure showed no tumor growth. The remainder of this desensitization was completed in the outpatient setting uneventfully. The ninth desensitization (12th cycle) also was completed in the outpatient setting without adverse reaction. The patient's magnetic resonance imaging showed a slight reduction in tumor size, and he has been stable since then (Figure 1). He is well clinically and remains fully functional.

Rapid drug desensitization has emerged as the standard of care for the management of patients with immediate hypersensitivity to first-line therapies. A number of mechanisms have been proposed to explain the temporary induction of tolerance in immediate HSRs. Although the clinical success of rapid desensitization protocols to treat delayed cutaneous eruptions to trimethoprim-sulfamethoxazole is well established, the pathophysiology that underlies desensitization for delayed-type HSRs remains unclear.⁷ In a report of a successful desensitization for fixed drug eruption to allopurinol, Teraki and Shiohara⁸

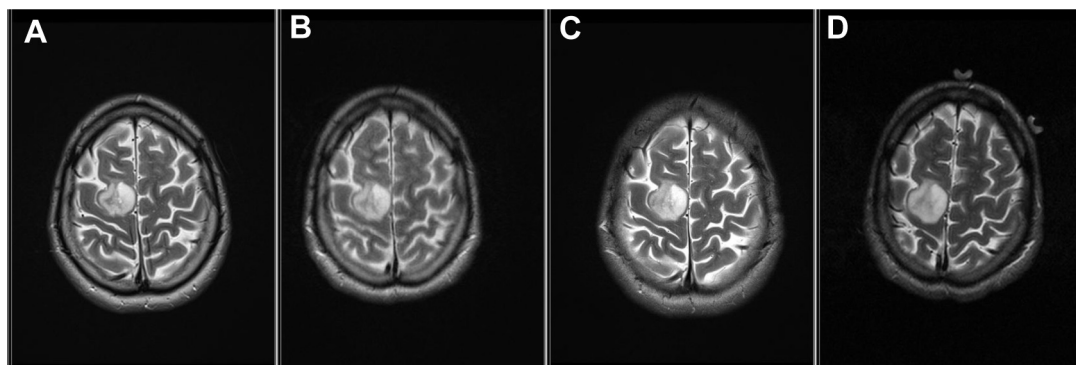


FIGURE 1. Nonenhancing hyperintense T2 mass in the posterior right superior frontal gyrus, just anterior to the paracentral gyrus. Pathology revealed oligoastrocytoma, World Health Organization grade II-III. (A) The mass after the 10th cycle of temozolomide: no tumor progression. (B) The mass after the seventh cycle: slightly decreased the tumor size. (C) The mass after the third cycle: stable tumor size. (D) The mass before treatment.

TABLE I. Comparison of desensitization protocols: custom solution that required inpatient care vs capsule, which enabled outpatient care

Custom solution* plus capsules†			Capsules only‡		
Step	Time (min)	Dose (mg)	Step	Time (min)	Dose (mg)
Day 1					
1	0	0.05*			
2	30	0.10*			
3	60	0.25*			
4	90	0.50*			
5	120	1.00*			
6	150	2.50*	1	0	5
7	180	5	2	45	5
8	210	10	3	90	10
9	240	20	4	120	20
10	270	40	5	150	40
11	300	50	6	180	50
12‡	330	60	7‡	210	60
Days 2-5 (same for both protocols)‡					
1	0	20§			
2	30	60			
3	60	60			
4‡	90	60			

*A temozolomide 5-mg capsule was opened and diluted in 100 mL of sterile water by the pharmacy; this yielded a solution with the concentration of 0.05 mg/mL that was used to prepare the doses that were less than 5 mg; these doses were drawn up in an oral syringe by the pharmacy and labeled accordingly.

†Commercially available 5-mg and 20-mg capsules were used for these protocols.

‡One to 3 subsequent doses of 60-65 mg given at 30-min intervals to reach therapeutic dose; final cumulative dose ranged from 250 to 325 mg as the therapeutic goal varied, depending on platelet count.

§The initial dose ranged from 10 to 25 mg, depending on the required amount to reach therapeutic goal of 250-325 mg, which varied depending on the platelet count.

postulate a role for induction of regulatory T cells that migrate to the affected area and suppress CD8⁺ activity, supported by flow cytometry analysis pre- and postdesensitization. It also is possible that steroid premedication promotes regulatory T-cell growth as well as suppresses hypersensitivity by other means and that steroids alone may be sufficient to ameliorate some

forms of delayed hypersensitivity. However, exciting new developments, including the recent effective use by Poreaux et al⁹ of a 12-step rapid desensitization protocol to treat generalized drug eruptions due to pegylated interferons, suggest an expanding role for these therapies for delayed HSRs independent of steroid use.

A recent report describes 2 successful rapid desensitizations for delayed cutaneous eruptions to temozolomide.⁴ However, these protocols are costly and labor-intensive because they typically necessitate hospital admission for appropriate facilities to compound sufficiently dilute solutions.^{2,6} Our success with the modified protocol suggests that outpatient desensitization by using commercially available formulations of temozolomide may be a safe and efficient option to treat HSRs to this essential medication.

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