Successful oral desensitization and reintroduction in selected glioma patients with procarbazine-mediated hypersensitivity

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LETTER TO THE EDITOR

Successful oral desensitization and reintroduction in selected glioma patients with procarbazine-mediated hypersensitivity

To the Editor

Oligodendrogliomas are rare, incurable primary brain tumors. Survival can be prolonged with neurosurgery and adjuvant chemoradiotherapy, including the PCV regimen consisting of procarbazine, lomustine, and vincristine. Unfortunately, side effects are common and many patients need dose reduction, therapy postponement, or incomplete cycles of PCV due to cytotoxicity, hepatotoxicity, and cutaneous eruptions.[1] Apart from these side effects, drug hypersensitivity reactions (DHR) may occur, particularly for procarbazine. There are no predictors for developing a DHR, but antiepileptic drugs are associated with an increased risk, possibly due to their hepatic enzyme-inducing properties.[1] Procarbazine may cause various types of DHR.[2,3] Maculopapular eruptions (MPE) are most frequently documented, but fixed drug eruption (FDE), urticaria, and toxic epidermal necrolysis, as well as pneumonitis, have been described.[2,4,5] These manifestations suggest that procarbazine-related DHR can be of IgE-mediated, T-cell–mediated, and possibly other mechanisms.

Procarbazine-related DHR is mainly a clinical diagnosis. Intracutaneous testing is not possible due to drug toxicity. Patch tests can be performed for nonimmediate DHR, but their predictive value remains unclear.[3] After a procarbazine-related DHR, discontinuation of therapy is advised.[2] There are no reports regarding reintroduction of procarbazine after occurrence of a severe DHR. For milder reactions such as MPE, a so-called treating through strategy may be employed, reintroducing procarbazine with concomitant use of antihistamines and corticosteroids.[6] While desensitization protocols are available for direct, IgE-mediated DHR against several other chemotherapeutics, no such protocols exist for procarbazine.

We here describe the evaluation of several patients referred for procarbazine-related DHR. Next, we explored the possibility of reintroducing procarbazine using both treating through and desensitization strategies. Between April 2018 and October 2019, six patients with procarbazine-related DHR were referred to our Allergology clinic (Table 1). All suffered from generalized cutaneous reactions without extracutaneous systemic involvement. In patients with a suspected nonimmediate DHR, patch tests with procarbazine 50 mg (Natulan; commercialized form used by the patients) in powder "as is," and 30% in aqua and 30% in petrolatum were performed and read at 20 minutes and at days 3 and 7. Patient A showed positive reactions to procarbazine 30% aqua and 30% pet at Day 3. She had a medical history of epilepsy and hypothyroidism for which she was treated with valproic acid and levothyroxine, respectively. Possibly, the concomitant use of valproic acid had increased her susceptibility for procarbazine-related DHR. The procarbazine was stopped, and she was treated with antihistamines, upon which the skin lesions resolved within 48 hours.

We developed a novel desensitization schedule for procarbazine for patient A, based on available schedules for other nonimmediate hypersensitivity reactions and our institutional experience (Table 2).[7,8] Three oral solutions of 0.1 mg/mL, 1 mg/mL, and 10 mg/mL were prepared, based on Lehmann *et al*[9] Procarbazine was gradually updosed in 12 steps over four consecutive days. No additional anti-allergic drugs were used during desensitization; nonetheless, the reintroduction remained uneventful and the third and fourth cycle of PCV chemotherapy could be successfully administered using this desensitization schedule. In the fifth cycle, procarbazine was stopped because of a severe thrombocytopenia. After six cycles, the MRI brain scan showed tumor reduction. A similar desensitization regimen was initiated in patient B but could not be evaluated properly, since it was prematurely aborted to due to cytotoxicity. Whether the recurrent prurigo without visible cutaneous abnormalities represented an early DHR relapse or was an unrelated finding remains speculative.

For two other patients, procarbazine could be reintroduced using a treating through strategy. Patient C had symptoms suggestive of a T-cell–mediated DHR but negative patch tests and preferred a regular reintroduction over the desensitization protocol. Her skin symptoms relapsed on Day 6 of the third cycle and prednisolone and antihistamines were started, which led to adequate symptom control. The reintroduction in patient E remained uneventful using prophylactic antihistamines.

Taken together, four of six patients with cutaneous procarbazine-related DHR were rechallenged. Two of them tolerated procarbazine with the use of anti-allergic medication; the two other patients were desensitized which was successful in one of them but

Abbreviations: DHR, drug hypersensitivity reaction; FDE, fixed drug eruption; MPE, maculopapular eruption; PCV, procarbazine, lomustine, vincristine; Pet, petrolatum.

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TABLE 1 Clinical characteristics of patients with procarbazine-related drug hypersensitivity reactions

Patient	Age (y)	Gender	Oncologic diagnosis	Start of allergic symptoms	Clinical symptoms	Patch tests	Course
A	55	F	IDH-1 mutated, 1p/19q-codeleted oligodendroglioma WHO2	Cycle 2, Day 11	MPE, pruritus scalp en legs	**Positive**[*,*]	Successful reintroduction via prolonged desensitization schedule without concurrent use of prophylactic anti-allergic medication
B	38	F	IDH-1 mutated, 1p/19q-codeleted oligodendroglioma WHO2	Cycle 2, Day 8	Pruritus and erythema hands, back, facial, and digital angioedema/ swelling	Negative	Unsuccessful reintroduction via intented prolonged desensitization schedule without concurrent use of prophylactic anti-allergic medication, stopped due to other toxicity; concurrent pruritus without visible cutaneous abnormalities
C	31	F	IDH-1 mutated, non codeleted astrocytoma WHO2	Cycle 2, Day 9	Pruritic erythematous plaques on eyelids, forehead, cheeks, and nose.	Negative	Recurrent symptoms after regular reintroduction, successfully countered upon adding oral prednisolone (30mg daily) and antihistamines (levocetirizine 10mg daily)
D	48	M	IDH-1/2 mutated, 1p/19q-codeleted oligodendroglioma WHO2	Cycle 2, Day 2	Generalized pruritus and MPE	Negative	Reintroduction not possible due to other toxicity
E	66	M	IDH-1 mutated, noncodeleted astrocytoma WHO 2	Cycle 3, Day 6	Pruritic erythematous rash trunk and extremities	N/A	Successful reintroduction with prophylactic use of antihistamines (levocetirizine 10mg daily)
F	25	M	IDH-1 mutated, noncodeleted astrocytoma WHO2	Cycle 3, Day 9	Generalized urticaria	N/A	Reintroduction refused by the patient

Abbreviations: F, female; IDH, isocitrate dehydrogenase; M, male; MPE, maculopapular eruption; N/A, not assessed; WHO, World Health Organization.

* 50 mg procarbazine in 30% aqua and 30% petrolatum at Day 3.

TABLE 2 Oral desensitization protocol for procarbazine 50 mg

Day	Time (hour)	Procarbazine (mg)	Procarbazine suspension		Cumulative dose (mg)
			mg/mL	volume	
Day −2	8.00	0.01	0.1 mg/mL	0.1 mL	0.01
	14.00	0.02	0.1 mg/mL	0.2 mL	0.03
	20.00	0.05	0.1 mg/mL	0.5 mL	0.08
Day −1	8.00	0.1	0.1 mg/mL	1 mL	0.18
	14.00	0.2	0.1 mg/mL	2 mL	0.38
	20.00	0.4	0.1 mg/mL	4 mL	0.78
Day 0	8.00	0.8	0.1 mg/mL	8 mL	1.58
	14.00	1.6	0.1 mg/mL	16 mL	3.18
	20.00	3.0	1 mg/mL	3 mL	6.18
Day 1[*,**]	8.00	6.0	1 mg/mL	6 mL	12.18
	14.00	12.5	1 mg/mL	12.5 mL	24.68
	20.00	25	10 mg/mL	2.5 mL	49.68
Day 2 to 14	8.00	50	50 mg tablet		

Note: Desensitization schedule that was used for patient A.

* At the end of Day 1, a cumulative dose of nearly 50 mg is reached. This was the planned dose for the second cycle because of thrombocytopenia at 100 mg/day during the first cycle. She received 50mg procarbazine daily in subsequent cycles until it was stopped completely in cycle 5.

could not be properly evaluated in the other patient. To our knowledge, this is the first description of a successful oral desensitization for T-cell–mediated DHR against chemotherapeutics.

Some limitations should be borne in mind. The predictive value of patch tests is not well-studied, and thus, both false-positive results due to irritant effects of the drug and false-negative results due to its immunosuppressive capacity may occur. The risk of eliciting a recurrent DHR after rechallenge is probably high but not entirely clear, since reintroduction of the drug is generally discouraged.[2] It is not impossible that patients C and E would have tolerated the procarbazine reintroduction without additional anti-allergic medication. Either way, these outcomes would also implore for reintroduction of procarbazine in patients in which this is desired and where the DHR is limited to mild-to-moderate skin reactions, making it an important finding for glioma treatment. The theoretical risk of eliciting a more severe DHR upon reintroduction should be considered but appears to be small in practice. Particularly for moderate and patch test-confirmed skin reactions, we recommend reintroduction using prolonged desensitization protocols. For type III reactions and other severe DHR, no recommendations can be made and avoidance probably remains the safest option. For immediate DHR, we would apply a different desensitization procedure which we to date have not been able to explore in clinical practice. Clearly, there is a need for reliable, preferably in vitro diagnostics in order to properly establish the diagnosis and to better understand the underlying immunological mechanism of procarbazine-related DHR. Furthermore, prospective clinical trials comparing drug rechallenge via desensitization or treating through strategies in patients with mild-to-moderate DHR would facilitate optimal clinical decision-making regarding potential drug reintroduction.

In conclusion, desensitization or reintroduction of procarbazine appears to be feasible and safe in patients with mild-to-moderate cutaneous DHR to procarbazine; additional studies in larger patient populations are required in order to make robust recommendations regarding the exact safety profile.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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