

Gerasimos Tsilimidos

Division and Central Laboratory of Hematology, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne

Alice Horisberger**Camillo Ribi**

Division of Immunology and Allergy, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland

Anne Cairol**Gregoire Stalder**

Division and Central Laboratory of Hematology, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne

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Successful Rapid Oral Desensitization to Ibrutinib in a Patient With Severe Immediate Hypersensitivity Reaction

Introduction

We report a case of oral desensitization to ibrutinib after a severe immediate hypersensitivity reaction in a patient treated for a primary central nervous system lymphoma (PCNSL).

Case Description

The patient was a 48-year-old woman who was diagnosed in December 2017 with a primary central nervous system lymphoma PCNSL after having persistent headaches and a hyposensitivity with paresis of the right side of her body. A magnetic resonance imaging (MRI) showed a primary mass in the anterior arm of the right internal capsule of the brain and a secondary mass in the right frontal white matter. Brain biopsy confirmed diagnosis of a diffuse large B-cell lymphoma of activated subtype (ABC).

Given her young age and the absence of comorbidities, high-dose chemotherapy according to the MATRix protocol (4 cycles) was given, followed by intensification with BCNU-thiotepa and autologous stem cell transplantation¹ and then a consolidation by whole brain radiotherapy with a boost on the right internal capsule. Complete remission was achieved for 10 months until relapse in February 2019. Second-line treatment associating rituximab and temozolomide² was administered, with a partial response for 6 months. After a second relapse in August 2019, we introduced ibrutinib at 560 mg/d.³ After 7 days of exposure, the patient developed a generalized maculopapular rash (Supplementary Figure 1),

palmoplantar hyperkeratosis, and erosions of the mouth mucosa with dysphagia. Infection was excluded. A skin biopsy showed perivascular superficial dermatitis with a few eosinophils without vasculitis. A grade 3 mucocutaneous toxicity owing to an off-target effect of ibrutinib on epidermal growth factor receptor (EGFR) was suggested.⁴ Ibrutinib was stopped and symptoms resolved. An MRI performed 13 days after ibrutinib initiation showed a greater than 50% regression of tumor lesions. Subsequently, nivolumab was introduced,⁵ but was rapidly stopped owing to grade 3 serositis with pericardial and pleural effusions and grade 3 hepatitis. The fifth-line treatment was initiated in October 2019 with rituximab and lenalidomide with complete response at 6 months.⁶ In June 2020, a follow-up MRI showed a new brain lesion on the left superior frontal gyrus.

After this third relapse, considering the lack of therapeutic alternatives and the response previously documented after only 1 week of treatment with ibrutinib, we decided to reintroduce ibrutinib. Because skin toxicity owing to EGFR inhibition is dose dependent, we opted for a rechallenge at 140 mg/d, based on the literature.⁷ Six hours after the first administration, the patient developed a pruritic macular rash with facial flush and edema (Figure 1), tongue swelling, and dyspnea. Clinical presentation was consistent with a severe immediate-type hypersensitivity reaction. The patient received intravenous steroids and antihistamines with a rapid resolution of symptoms. There was no increase in the serum tryptase.

In the absence of alternatives, we designed a 12-step desensitization protocol with a target dose of 140 mg of ibrutinib (Table 1), based on published reports of rapid tolerance induction in drug hypersensitivity⁸ and successful rapid oral desensitization with crizotinib (ALK inhibitor).⁹ Oral antihistamines were given 12 hours and

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Address for correspondence: Gerasimos Tsilimidos, Division and Central Laboratory of Hematology, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland.

E-mail contact: gerasimos.tsilimidos@chuv.ch

Table 1 Rapid Oral Desensitization Protocol for Ibrutinib

Dose Number	Ibrutinib Concentration (mg/mL)	Time Observed After Each Dose (min)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	0.03	15	1.25	0.0375	0.036 0
2	0.03	15	2.50	0.0750	0.1140
3	0.30	15	0.50	0.1500	0.0264
4	0.30	15	1.00	0.3000	0.5640
5	0.30	15	2.00	0.6000	1.1640
6	3.00	15	0.40	1.2000	2.3640
7	3.00	15	0.80	2.4000	4.7640
8	3.00	15	1.60	4.8000	9.5640
9	3.00	15	3.20	9.6000	19.1640
10	3.00	15	6.25	18.7500	37.9140
11	3.00	15	12.50	37.5000	75.4140
12	3.00	15	25.00	75.0000	150.4140

Figure 1 Severe facial edema 6 hours after ibrutinib rechallenge.

1 hour before protocol initiation. The desensitization was initially well tolerated, but 6 hours after the target dose was achieved, the patient developed an acute dyspnea with facial edema and generalized pruritus. She received intramuscular epinephrine, intravenous glucocorticoids and antihistamines. The protocol was repeated 24 hours after symptom resolution, this time without any reaction. The patient was discharged with an oral dose of 140 mg of ibrutinib. Doses were thereafter doubled once every week up to a dose of 420 mg, without the recurrence of hypersensitivity. Ibrutinib was well-tolerated aside from mild xerosis with exfoliation on the hands and feet that was attributed to off-target EGFR inhibition.⁴ The first MRI, 1 month after the target dose was reached, showed a partial response with almost 50% regression of the left superior frontal gyrus lesion. Signed informed consent was obtained from the patient included in this work.

Discussion

Ibrutinib is the first Bruton's tyrosine kinase (BTK) inhibitor approved by the US Food and Drug Administration and by the European Medicines Agency for many indolent lymphomas as well as diffuse large B-cell lymphoma especially the activated subtype (ABC) and primary central nervous system lymphoma. BTK participates in intracellular pathways involving cell migration, survival, and proliferation. It is activated by BCR stimulation and plays an important role in the survival of neoplastic B cells.¹⁰ Ibrutinib binds irreversibly to cysteine residue 481 within the adenosine triphosphate binding domain of BTK. Although it is selective for BTK, it can have significant off-target activity against other kinases, including BMA, BLX, EGFR, HER2, ITK, JAK3, and TEC kinases, which all contain a cysteine residue similar to 481 of the BTK. Off-target activity is responsible for most side effects¹¹ with the commonest being hypertension, atrial arrhythmias, bleeding events, diarrhea, hematotoxicity, and infections.¹²

Cutaneous side effects are reported in 2%–27% of patients on ibrutinib treatment, most frequently bruises or petechiae, and occasionally other skin rashes.¹³ Various cutaneous patterns are described after ibrutinib exposure, such as maculopapular rash, eczema, acne, palpable purpura, and pityriasis rosea.^{4,7,12} They are mostly attributed to off-target EGFR, HER-2, and c-KIT inhibition.⁴ Our patient presented initially with a mucocutaneous toxicity similar to those reported in patients treated with EGFR inhibitors.¹⁴ Grades 1 or 2 rashes do not need special management or dose adjustments. In our patient, the severity of the skin toxicity forced withdrawal of the drug. Newer and more selective BTK inhibitors, such as acalabrutinib or zanubrutinib, might have a lower incidence of skin toxicities, although recurrence with acalabrutinib has been described.⁴ These 2 drugs have not been approved yet in Europe and thus they were not a feasible option for our patient.

Upon ibrutinib rechallenge at lower doses, our patient developed a different reaction characterized by a rapid onset and anaphylactic symptoms. We observed resolution in less than 1 hour after antiallergic treatment. This immediate drug hypersensitivity occurred within a few hours after exposure and was previously reported in

patients upon ibrutinib reexposure.⁷ Subsequent rechallenges were performed under high doses of corticosteroids tapered off over 8 to 12 weeks. Desensitization with ibrutinib was previously reported in an 18-step strategy for a patient with a pruritic rash.¹⁵ Although the details on the type and severity of the reaction are lacking, no symptoms of the anaphylaxis are reported.¹⁵ In contrast, our patient presented a severe immediate-type reaction. We performed a 12-step desensitization that we needed to repeat twice to enable tolerance. The underlying mechanism of this immediate reaction is unknown. IgE-mediated hypersensitivity could be supported in a previously sensitized patient. A nonspecific activation of mast cells and eosinophils in a previously injured skin is a second hypothesis.

This case demonstrates that a rapid oral desensitization procedure for ibrutinib may be performed after a severe immediate reaction, saving the patient from a long course of oral steroids and ensuring ibrutinib continuation.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.clml.2021.05.014](https://doi.org/10.1016/j.clml.2021.05.014).

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Supplementary Figure. Generalized maculopapular rash after seven days of treatment with ibrutinib.

