

Letter to the Editor

Hypersensitivity reactions to racemic calcium folinate (leucovorin) during FOLFOX and FOLFIRI chemotherapy administrations

To the Editor:

Hypersensitivity reactions (HSRs) to antineoplastic agents are an increasingly important problem, and some patients may be doomed to therapy discontinuation for fear of inducing severe reactions.¹ HSRs to oxaliplatin have been reported, with the incidence ranging from 12% to 17%,¹ whereas very few cases of folinic acid HSRs have been reported.² Folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) and folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI) regimes are used in colorectal cancer treatment.² In these regimes, folinic acid and oxaliplatin (or irinotecan) are usually administered simultaneously; therefore, in the case of HSRs to folinic acid, some may assume that the patient is experiencing an HSR to another likely medication such as oxaliplatin.²

Folinic acid is administered in our hospital as racemic calcium folinate (leucovorin). We retrospectively searched data of patients presenting with HSRs to chemotherapy including leucovorin, from January 2013 to January 2014, in the Desensitization Program database of the Ramon & Cajal University Hospital Allergy Division (which includes data from all patients referred for assessment after suffering an HSR to antineoplastic agents in this hospital). Drug provocation tests (DPTs) with leucovorin are performed systematically in our assessment protocol whenever leucovorin is included in the chemotherapy regime. During a 12-month period, 44 patients were assessed after suffering an HSR to a chemotherapy regime including leucovorin (35 FOLFOX; 9 FOLFIRI), and 5 of them were confirmed as leucovorin-reactive patients.

First case: 65-year-old man, stage IV gastric adenocarcinoma, FOLFOX treatment. He presented, during his first administration, with facial erythema and general urticaria 30 minutes after oxaliplatin/leucovorin was initiated.

Second case: 66-year-old woman, stage IV colon adenocarcinoma, FOLFOX treatment. She presented, during her 18th administration, with genital and scalp itching, rhinoconjunctivitis, and general malaise 50 minutes after oxaliplatin/leucovorin was initiated. The patient suffered unreported milder symptoms (limited general itching) during the previous administration.

Third case: 52-year-old woman, stage IV rectal adenocarcinoma, FOLFOX treatment. She presented, during her 19th administration, with intense chills 70 minutes after oxaliplatin/leucovorin was initiated. The patient suffered unreported milder symptoms (mild chills) during the previous administration.

Fourth case: 73-year-old man, stage IV colon adenocarcinoma, FOLFIRI treatment. He presented, during his first administration, with facial erythema, general urticaria, and eyelid angioedema 20 minutes after the infusion of irinotecan/leucovorin was initiated.

Fifth case: 80-year-old woman, stage IV colon adenocarcinoma. She received 10 FOLFOX administrations but discontinued because of blood-cell toxicity. She started FOLFIRI and, during her 8th administration, presented with dyspnea, chest pain, oxygen desaturation (85%), and facial erythema 10 minutes after

irinotecan/leucovorin was initiated. She suffered unreported milder symptoms (limited chest pain) during the previous administration.

All patients were referred to our Desensitization Program. Trained personnel in adequate settings performed skin testing at least 2 weeks after the initial reaction to minimize false-negative results.¹ Skin tests (prick and intradermal) were performed and assessed according to previous studies.¹ Patients with negative skin test results were subjected to DPT: administering the desired full dose of the culprit drug according to manufacturer instructions.¹ The DPT result was considered positive when it reproduced the original symptoms or showed an objective HSR.¹ L-isomer calcium folinate is the purified single-enantiomer version of leucovorin, and it has been used with similar efficacy.³ To our knowledge, no reactions to L-isomer calcium folinate had been reported, and so we decided to test tolerance to this form of folinic acid as a possible therapeutic alternative. Results are presented in Table I.

Cases 1 through 4 decided to avoid leucovorin. Case 5 decided with her oncologist to go on with FOLFIRI. We programmed a rapid desensitization to leucovorin. A case of oral leucovorin desensitization has been previously described,⁴ but diagnosis of hypersensitivity was not confirmed by DPT in that patient.⁴ Thus, we chose the (*in vitro* and *in vivo* validated) Brigham and Women's Hospital protocol,⁵ which we have previously used for other medications lacking published series of desensitized patients.⁶ The patient received the medication's full therapeutic dose by rapid desensitization, and she experienced no breakthrough reactions. She could safely continue with FOLFIRI treatment.

Even if few HSRs to leucovorin have been reported, we found a prevalence, during a 12-month period, of 11% (95% CI, 1.98%-20.74%) in our population of FOLFOX/FOLFIRI-reactive patients. HSRs to leucovorin may be more frequent than it seems. We believe that leucovorin may act as a confusion factor. It has even been reported as a cause of recurring reactions to oxaliplatin, due to an incomplete diagnosis in which leucovorin had been overlooked.²

Case 3 suffered chills, back pain, elevated blood pressure, and fever. Case 5 suffered chills during DPT. Similar atypical symptoms have been reported in a leucovorin-reactive patient² and also in an oxaliplatin-reactive patient, in whom desensitization was also considered.⁷ The mechanisms of these reactions remain unknown.

Case 1 had a reaction during his first administration, and so sensitization to leucovorin may not necessarily need several exposures but may be acquired by other unknown mechanisms. All our patients had negative skin test results. One report shows positive skin test results to leucovorin, followed by positive DPT result, in a folic acid-reactive patient⁸; however, the clinical value of skin tests with leucovorin is yet to be established.

All our patients tolerated ingestion of foods containing natural folates and rejected DPT with folic acid. Cross-reactivity has been reported between folinic acid and folic acid,⁸ and so we believe that folic acid (as in vitamin supplements) in leucovorin-reactive patients should be allowed only after ruling out cross-reactivity by negative DPT result. All leucovorin-reactive patients who underwent DPT with L-isomer calcium folinate had a reaction. Even if 2 patients rejected this DPT, we believe that L-isomer

TABLE I. Results of allergy workup in our leucovorin-reactive patients

Patients	ST to oxaliplatin/irinotecan	ST to both leucovorin and L-isomer calcium folinate	DPT with leucovorin	Tryptase levels during DPT with leucovorin (60 min after reaction) (ng/mL)	DPT with L-isomer calcium folinate	DPT with oxaliplatin/irinotecan
Case 1	Negative	Negative	Positive: urticaria	1.87	Positive: urticaria	Negative
Case 2	Negative	Negative	Positive: general urticaria, rhinoconjunctivitis	3.04	Positive: general urticaria, rhinoconjunctivitis, shortness of breath	Negative
Case 3	Negative	Negative	Positive: chills, back pain, elevated blood pressures, fever	2.46	Not performed	Negative
Case 4	Negative	Negative	Positive: general urticaria, eyelid angioedema	4.85	Not performed	Negative
Case 5	Negative	Negative	Positive: chills, chest pain, facial erythema	1.23	Positive: chills, facial erythema	Negative

ST concentrations used for oxaliplatin were 5 mg/mL and 0.5 mg/mL.¹ For irinotecan (20 mg/mL; 2 mg/mL), leucovorin (10 mg/mL; 1 mg/mL), and calcium levofolate (10 mg/mL; 1 mg/mL) were empirically obtained: full-strength solution according to manufacturer instructions and diluted further in normal saline to 1:10, and these concentrations were tested in 10 control patients to prove them nonirritant.

ST, Skin test.

calcium folinate may not be a good alternative in leucovorin-reactive patients; however, more studies are needed to clarify the mechanisms and clinical relevance of these findings. Anyhow, we believe that the use of L-isomer calcium folinate in leucovorin-reactive patients should be allowed only after confirming tolerance by means of a negative DPT result.

Our patients could continue their therapy either by avoiding leucovorin or by rapid desensitization (with adequate installations, standardized protocols, and expert personnel).

Up to 3 patients suffered overlooked milder symptoms during previous administrations. Helping patients identify and communicate these symptoms may prevent unnecessary risks.

In conclusion, we describe an important number of confirmed HSRs to leucovorin during a 1-year period. We show how patients reacting to leucovorin may also react to L-isomer calcium folinate. We believe that protocols studying FOLFOX/FOLFIRI HSRs should be undergone by drug allergy experts, and include systematic skin testing and DPT with folinic acid, to avoid infra-diagnosis and its resulting risks. Moreover, we report the first intravenous rapid desensitization to leucovorin in a reactive patient (confirmed by DPT).

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Alicia Ureña-Tavera, MD*

Miriam Zamora-Verduga, MD*

Ricardo Madrigal-Burgaleta, MD

Denisse Angel-Pereira, MD
 Maria Pilar Berges-Gimeno, MD, PhD
 Emilio Alvarez-Cuesta, MD, PhD

From the Allergy Division, Ramon & Cajal University Hospital, Madrid, Spain. E-mail: rmadbur@hotmail.com.

*These authors share first-author credit.

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