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Letter to the Editor

Hypersensitivity reactions and drug fever by bendamustine: A case report of three patients

Dear Editor

Bendamustine is an intravenously-administered alkylating agent approved as monotherapy or in combination with other agents for the treatment of refractory hematologic malignancies, such as chronic lymphocytic leukemia (CLL) and B-cell non-Hodgkin lymphoma.[1,2] Despite bendamustine is well-tolerated, it can provoke allergic reactions as well as drug fever.[3,4] To our knowledge, there are not reported cases of immunological reactions with an allergological study carried out.

We present three patients diagnosed with B-cell CLL (B-CLL) treated with bendamustine as monotherapy suffered from hypersensitivity reactions. *Patient 1:* A 61-year-old woman, diagnosed with B-CLL received bendamustine, tolerating the first cycle. Three weeks later, 8 h after the 1st dose of the 2nd cycle, she suffered throat discomfort, pruritus, hives, general erythema and facial swelling; which disappeared within 24 h after treatment. *Patient 2:* A 61-year-old man, diagnosed with B-CLL. Four years ago, he adequately tolerated bendamustine. One week later after the 1st and well tolerated cycle, he received the 2nd one and 8–10 h after the dose he developed a maculopapular exanthema, edema in arms and legs, along with desquamation of hands and feet, without residual lesions. Symptoms disappeared within the first 2 weeks. *Patient 3:* A 63-year-old man, diagnosed with B-CLL. Three hours after the infusion of the 1st and 2nd cycles of bendamustine, he had generalized tremor and fever of 39 °C. The symptoms ceased with acetaminophen 650 mg. One month later, 3 h after the 3rd cycle of bendamustine, he had generalized tremor and erythema, dizziness and body temperature of 39 °C. Hypotension, paroxysmal atrial fibrillation and a mild renal failure were verified. The symptoms disappeared with acetaminophen 1gr and an adequate hydration.

We performed skin-prick-test (SPT) at 1 mg/ml and intradermal testing (IDT) at 0.001, 0.01, 0.1 and 1 mg/ml, with immediate (at 20 min), late (before 12 h), and delayed (at 24 h and 72 h) readings. As negative controls three B-CLL patients underwent SPT and IDT with negative results. These different concentrations did not provoke neither cutaneous necrosis nor hyperpigmentation. *Patient 1.* SPT was negative. IDT at 0.1 and 1 mg/ml were positive at 24 h, being negative 72 h later (Fig. 1). Of note, although the positivity of the IDT was detected at 24 h, the maximum expression of intensity was produced at home between 6 and 10 h (late response) after finishing skin tests in our outpatient clinic. The rest of the tests were negative. *Patient 2.* He had a negative SPT. The 24 h readings of the IDT were positive at 0.01, 0.1 and 1 mg/ml, remaining positive 72 h later (Fig. 2). The rest of the tests were negative. *Patient 3.* The SPT and IDT (immediate and delayed readings) were negative.

In this work, we report the first two cases of reactions to bendamustine with a positive result for the IDT in the allergological study carried out, which demonstrated a hypersensitivity to bendamustine. We also report the first case of drug fever induced by bendamustine in clinical use, where the work-up carried out did not demonstrated neither a type I nor a IV hypersensitivity mechanism to this drug.

Clinically, the cutaneous reactions expressed on the patients ≠1 and ≠2 are justified by different mechanisms. In fact, patient ≠ 1 suffered from a typical IgE-mediated reaction (Type I hypersensitivity reaction) revealed by means of a positive IDT in its late reading (another kind of immediate reading). Nevertheless, patient ≠2 suffered from a typical maculopapular exanthema with an associated edema on arms and legs revealed by means of a positive IDT in its delayed reading to three different concentrations, remaining positive 72 h later. In this case, we think that this cutaneous reaction could be produced by Th2 cells with/without eosinophils and/or IL-4, IL-5, IL-13 secretion (Type IVb hypersensitivity reaction), often associated with an IgE-mediated type I reaction, which would justify the associated edema. Other possibility would be a direct T-cell stimulation by means of perforin/granzyme B from cytotoxic lymphocytes (Type IVc hypersensitivity reaction).[5]

Drug fever is a common condition that is frequently misdiagnosed, being a diagnosis of exclusion.[6] A febrile response that coincides temporally with the administration of a drug, disappears after discontinuation of the offending agent, and reappears after a new administration, constitutes the unique diagnostic criterion.[7] In nonsensitized individuals receiving a drug for the first time, the onset of fever is highly variable.

There are different mechanisms provoking fever induced by drugs in oncologic patients: neutropenic fever (or febrile neutropenia), infectious fever, tumor fever, blood transfusion fever, and drug fever (early or later).[8] In drug fever, a stimulation of cytokines (IL-6, TNF-α), as well as immune complex aggregation are involved.[5] The use of antineoplasic chemotherapy or the neoplasia itself may provoke drug fever by neoantigens production. In any case, this would be attributed to a type IIa hypersensitivity reaction, where complement proteins or IgG/IgM antibodies are implicated.[9] It is also possible that drug fever may be due to a systemic reaction by immune complex, complement activation and/or neutrophil recruitment, that is, a type IIIb hypersensitivity reaction, being involved either complement or antigen and IgG.[9] The patient ≠3 did not exhibit any feature of vasculitis, glomerulonephritis, peripheral

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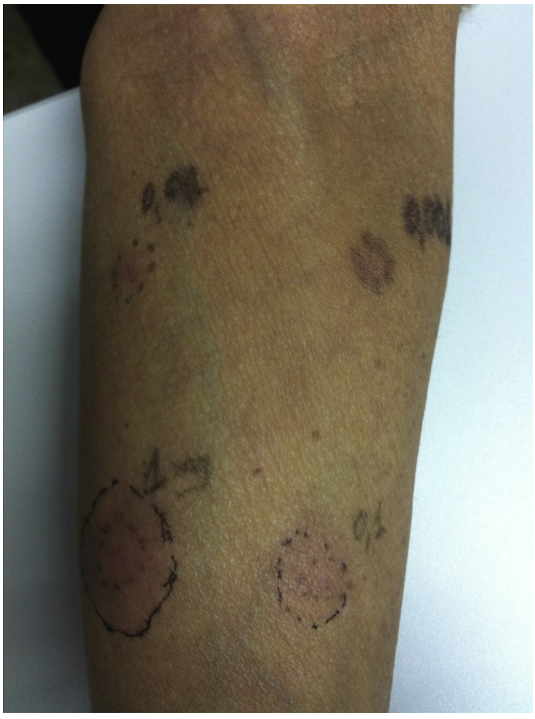

Fig. 1. Lectures of the intradermal tests with bendamustine at 24 h: negative at 0.001 and 0.01, and positive at 0.1 and 1 mg/ml.

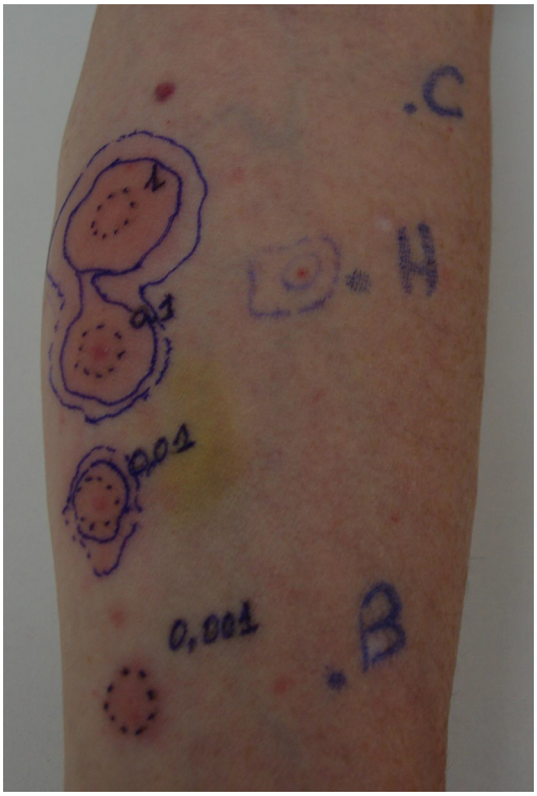

Fig. 2. Lectures of the intradermal tests with bendamustine at 24 h: negative at 0.001 and positive at 0.01, 0.1 and 1 mg/ml.

neuropathy, hematologic abnormalities (as thrombocytopenia), hypocomplementemia or abnormal liver function tests, as it can appear in serum sickness and systemic erythematosus lupus.[7] Furthermore, we suspect that a type IIa hypersensitivity mechanism should justify the cases of drug fever happened after the first doses of the drug in the life of the subject, due to the involvement of IgM instead of IgG, as it may occurred to our patient (a nonsensitized individual). Unfortunately, due to a lack of facilities, anti-bendamustine IgG or IgM antibodies and/or a validated basophil activation test could not be tested and so, this proposed mechanism could not be established conclusively.

On the other hand, some cases of bendamustine-induced fever have been described, all of them in clinical trials (phases I to III), using different high doses of this drug, ranging from 80 to 100 mg/m^2, and with a variable incidence of 3–40% of cases.[3,4,10] The patient ≠3 suffered from fever after doses of 70 mg/m^2 in three consecutive occasions. To accomplish this treatment regimen, he needed a pretreatment with dexamethasone 16 mg just previously the perfusion plus ranitidine and aspirine from 24 h before it, showing no new reaction.

To the best of our knowledge, we present the first three-case report of reactions by bendamustine wherein an allergological workup has been performed. Two patients suffered from immediate and delayed cutaneous hypersensitivity reactions, respectively, and the other one from a bendamustine-induced fever. Further studies are needed in order to clarify the true immunopathogenesis in these reactions, particularly in the latter entity.

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Conflict of interest

The authors have no conflict of interest to declare.

José Barbarroja-Escudero [a,*], Maria-Jose Sanchez-Gonzalez [a], Dario Antolin-Amerigo, Mercedes Rodriguez-Rodriguez, Melchor Alvarez-Mon

Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Madrid, Spain

* Corresponding author. Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Universitario Príncipe de Asturias, Universidad de Alcalá, Madrid, Spain.
E-mail addresses: jose.barbarroja@gmail.com, jose.barbarroja@uah.es (J. Barbarroja-Escudero).

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[a] José Barbarroja-Escudero and Maria-Jose Sanchez-Gonzalez contributed equally to the completion of this article and are both first authors.

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