Rapid desensitization for chlorambucil drug fever

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Chlorambucil is an oral alkylating agent, introduced in 1953, that is still used as a primary treatment for chronic lymphocytic leukemia (CLL).[1] Chlorambucil is usually well tolerated and often administered intermittently, with intervals of months or years between recurrent courses of treatment. Chlorambucil-induced drug fever presents as fever, rigors, and malaise within hours to days of starting chlorambucil, often after a drug-free interval. Some patients also develop skin rash, lymphadenopathy and systemic symptoms including vomiting, diarrhea and hypotension. Unlike sepsis, all symptoms remit when the drug is withdrawn and recur within approximately the same time frame when the drug is reintroduced.[1,3] Once drug fever has been diagnosed, most clinicians discontinue chlorambucil from the treatment regime and use alternate chemotherapeutic agents. There is one report of slow desensitization to chlorambucil, which was carried out over a two to three month period.[2]

We report a more rapid desensitization to chlorambucil in three patients with typical drug fever and propose this as a reasonable, safe and well-tolerated alternative to removal of chlorambucil from the therapeutic regime.

Three patients (2 females, age range 69 to 88) were referred to the Drug Safety Clinic for assessment of febrile reactions to chlorambucil. Past histories (hypertension, dyslipidemia, arthritis, asthma, hiatus hernia) were noncontributory and concomitant medications (ramipril, hydrochlorothiazide, ASA, nifedipine, rabeprazole) were unchanged for years. One patient was receiving chlorambucil for Waldenstrom's macroglobulinemia, whereas the other two were being treated for CLL. One patient had received multiple courses of chlorambucil intermittently over 8-10 years before he reacted adversely. The others reacted on their first exposure. All patients had high fever and shaking chills. Other symptoms included malaise, weakness, nausea, dizziness and/or a pruritic rash. Sepsis and other causes of fever were appropriately investigated with blood and urine cultures, CXR, and extensive serology, and were ruled out. One patient received a course of antibiotics empirically. The onset of symptoms varied from 4 hours to 4 days after starting chlorambucil, but symptom resolution occurred consistently within 24 to 48 hours following drug withdrawal. Chlorambucil rechallenge in two of the three patients resulted in the return of the same symptoms within the same time frame.

Chlorambucil was reintroduced to all three patients using a desensitization schedule. All were started on 0.5 mg of chlorambucil daily and increased to 2 mg, with 0.5 mg increases occurring approximately every 5 days. One patient successfully increased the dosage to 4 mg by continuing to increase by 0.5 mg every 7 days. Two patients attempted to increase directly from 2 to 3 mg, but only one was able to tolerate it. Two patients have remained on chlorambucil 3 and 4 mg daily for 4 and 11 months, respectively. The other patient was not restarted on treatment, as his white cell count has remained sufficiently low for over one year. The first published desensitization to chlorambucil 2 mg took 2 to 3 months.[2] In contrast, all three of our patients were successfully desensitized to chlorambucil 2 mg within 15 days and were then able to gradually increase to higher doses as needed. As in any desensitization, our procedure was individualized according to each patient's tolerance. It is important to note that the desensitized state will only be maintained for as long as the patient remains on the drug without any missed doses.4 If the medication is stopped for more than two or three days, the desensitization will have to be undertaken once again to avoid recurrence of the drug fever.

Desensitization is a technique of gradual reintroduction of the culprit agent. This was originally designed to allow patients to tolerate a medication to which they were considered allergic (e.g., IgE-mediated penicillin reactions). Since then, desensitization has also been utilized successfully in non-allergic, non-life threatening reactions, such as allopurinol rashes. This report expands the role of desensitization to patients with chlorambucil-induced drug fever and offers a reasonable alternative to removal of chlorambucil from the therapeutic regime.

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References

1. Levin M, Libster D. Allergic reactions to chlorambucil in chronic lymphocytic leukemia presenting with fever and lymphadenopathy. Leukemia Lymphoma 2005;46:1195-7.
2. Sawitsky A, Boklan BF, Benjamin Z. Drug fever produced by chlorambucil. New York State J of Med 1971;15:2434-6.
3. Zervas J, Karkantaris C, Kapiri E, et al. Allergic reactions to chlorambucil in chronic lymphocytic leukemia: case report. Leukemia Research 1992;16: 329-30.
4. Castells M. Desensitization for drug allergy. Curr Opin Allergy Clin Immunol 2006;6:476-81.