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Cutaneous Reactions after Treatment with 2-Chlorodeoxyadenosine

PHILIPPE MEUNIER[1], SYLVIE CASTAIGNE[2], JEAN-NOEL BASTIE[2], OLIVIER CHOSIDOW[3] and SELIM ARACTINGI[1]

[1]Department of Dermatology, Tenon Hospital, [2]Department of Hematology, Saint-Louis Hospital, Paris, France, [3]Department of Médecine, Pitié-Salpêtrière Hospital, Paris, France

2-chlorodeoxyadenosine (2-CdA) is a new purine analogue which has shown great efficacy in the treatment of hairy cell leukemia. Only one case of cutaneous reaction after this treatment has previously been reported.

The data from 33 patients treated with 2-CdA were retrospectively reviewed. Seven of these (21%) developed a disseminated eruption during the month following 2-CdA. One had toxic epidermal necrolysis. A reaction to the associated antibiotic therapy seemed "likely" or "very likely" in 5 out of the 7 cases. The incidence of adverse drug reactions may be increased after 2-CdA, and the role of CD4+ lymphocytopenia in these reactions is discussed. ***Key words: 2-CdA; HCL; skin manifestation.***

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S. Aractingi, Unité de Dermatologie, Hôpital Tenon, 4, rue de la Chine, 75020 Paris, France.

The ability of 2-chlorodeoxyadenosine (2-CdA) (cladribine, Leustatin, Ortho Biotech) to induce complete and long-lasting remissions in the majority of patients with hairy-cell leukemia (HCL) constitutes a major advance in the treatment of this disease (1). Besides its great therapeutic efficacy, 2-CdA has an innovative mode of administration, namely, a single course of treatment as an intravenous infusion lasting 1 week. In view of its efficacy and its ease of administration, 2-CdA has emerged as an important treatment option for HCL and may represent a future therapeutic tool in other lymphoproliferative diseases. Side effects of 2-CdA are essentially moderate myelosuppression and infections in which an organism is rarely isolated (2). Cutaneous adverse reactions have been reported in only one patient after 2-CdA treatment (3). We present here a retrospective study of clinical, biological and pathological parameters of cutaneous eruptions occurring after 2-CdA treatment for HCL.

MATERIAL AND METHODS

Thirty-three patients presenting with HCL at the two participating centres were included in a 2-CdA trial from January 1992 to August 1993. A requirement for eligibility to the trial was that patients must have had at least one poor prognostic criterion for HCL (4). There were 28 men and 5 women. Patients ranged in age from 34 to 82 years, with a median of 60.4 years. All patients received daily intravenous continuous infusion of 2-CdA 0.1 mg/kg/day for 7 days. Antibiotic treatment was given to 19/33 (58%) patients during the study period.

We retrospectively analyzed the data from patients presenting with any skin manifestation between the beginning of 2-CdA until the end of the first month after chemotherapy. The following parameters were studied: sex, age, clinical features, delay between chemotherapy and onset of eruption, white blood cell count on the first day of the eruption, skin biopsy results, including immunohistochemistry, other drug treatment, body temperature and clinical evolution. The intrinsic imputability score of drugs was studied (5).

RESULTS

Seven patients (21%) developed cutaneous manifestations. All were males. The median age was 63 years (55–69). HCL was present for a mean duration of 9 years (0.2–21). Lesions consisted of a maculo-papular exanthem in 6 patients and toxic epidermal necrolysis (TEN) in one. Manifestations appeared after a mean delay of 15.6 days (7–31) post 2-CdA. The clinical course was uncomplicated in all but one, who had fatal TEN. Median WBC at the onset of the eruption was 3.0×10^9/l (1.4–32). Of note, hypereosinophilia (0.748×10^9/l) and lymphocytosis (30.8×10^9/l) were each observed in one case (cases no. 6 and 1). Skin biopsies revealed dermal, pericapillary, lymphocytic infiltration in all cases; necrotic or vacuolized keratinocytes in three samples and only spongiosis with exocytosis in one. Immunohistochemical studies were performed in 3 patients; the infiltrate was predominantly composed of CD4+ cells in 2 cases and of a mixture of CD4+ and CD8+ cells in one. These cells were CD25-CD54+, CD58+, HLA DR+. The intrinsic imputability scores of the associated antibiotics were "very likely" in 4 cases (cases 2–5) and "likely" for sulfonamide in case 7, who had TEN, which represents 5 out of the 19 patients who received antibiotics (26.3%). In only 2 cases (cases 1 and 6) no other drug than 2-CdA was given. In case 1, characterised by a CD8 lymphocytosis, viral serological tests were negative (coxsackie-virus, echovirus, hepatitis B and C, parvovirus B19, HTLV1, CMV). In contrast, hepatitis C virus antibodies were detected 8 weeks after the cutaneous symptoms in case 6, while they were absent before.

DISCUSSION

HCL is a rare lymphoproliferative disorder of B-cell lineage, characterized by infiltration of the bone marrow with mononuclear cells, presenting irregular cytoplasmic projections (6). Recently, the use of 2-CdA has come to the fore in the treatment of HCL. 2-CdA is particularly interesting because complete remission rates of more than 80% after a single course have been reported (3, 7–9). 2-CdA is a purine analogue resistant to adenosine deaminase. The best clinical results have been obtained in HCL, but 2-CdA is also effective in patients with chronic lymphocytic leukemia (10) and in cases of refractory low-grade lymphoma (11). The toxicity of 2-CdA given as a single course is low. There is a transient marrow suppression with a WBC nadir after 8 days and median hematological recovery after 2 months.

We observed cutaneous eruptions in 21% of the 2-CdA-

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treated patients with HCL. In contrast, most series do not mention any cutaneous manifestations after 2-CdA (7–9). In one trial, only one case out of 26 treated patients had cutaneous manifestations (3). The lymphocyte recovery phenomenon is one of the major causes of cutaneous, disseminated eruptions after chemotherapy and is considered to be due to the peculiar properties of bursting mononuclear cells homing abnormally to the skin after aplasia (12). Since other series of patients with the same disease and the same chemotherapy do not report lymphocyte recovery, it is unlikely that this mechanism is implicated in the pathogenesis of the majority of the exanthems we observed. Furthermore, the contrast between the incidence of the eruptions observed after 2-CdA in literature and that observed in this study raises the question of the role of factors others than 2-CdA in the development of these rashes. Indeed, an adverse drug reaction to a drug other than 2-CdA was "very likely" or "likely" in 5 cases (patients 2–5, 7), suggesting that the majority of the cutaneous eruptions in our series could be the consequence of an adverse drug reaction to one of the associated treatments. This hypothesis fits well with the lower rate of cutaneous reactions reported in the literature, in which additional drugs were given in only 42% of patients in contrast with 58% of our cases.

Adverse drug reaction incidence in our series (26.3%) seems to be higher than that observed in the general population treated with amoxicillin or sulfonamides (5.1 and 3.3%, respectively) (13). 2-CdA induces abnormally prolonged CD4+ lymphocytopenia (14), greater than that observed with other chemotherapeutic agents (15). In HIV infection, the incidence of cutaneous adverse drug reaction parallels the decrease in the CD4 count (16). It has recently been proposed that these eruptions could be the consequence of a drug-induced T cell imbalance, leading to a cytotoxic reaction against virus-infected cutaneous cells (17). In view of the peculiar CD4 lymphocytopenia after 2-CdA, a similar mechanism could be involved in our patients. Caution is needed when prescribing treatments to patients after a course of 2-CdA.

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