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Hypersensitivity reactions to deoxycoformycin

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Summary. Deoxycoformycin (dCF) is a promising new antineoplastic agent in the treatment of lymphoid malignancies, particularly hairy cell leukemia (HCL). Skin toxicity in the form of a maculopapular eruption has previously been reported but has not clearly been associated with idiosyncratic reactions. We present five cases of dCF-related hypersensitivity reactions in which additional systemic manifestations indicated an allergic etiology. The value of dCF in treating lymphoid neoplasms suggests that further study of the treatment of these reactions is indicated.

Introduction

Although all classes of cytotoxic drugs have been reported to produce hypersensitivity reactions, the latter seem to be particularly frequent with drugs derived from microbial and plant sources [18, 19, 26, 27]. 2′-Deoxycoformycin (dCF; Pentostatin, NSC 218321) is an antibiotic produced by culture broths of *Streptomyces antibioticus* now in wide use as an antineoplastic agent [29]. Early studies suggest that dCF, an inhibitor of adenosine deaminase, is active in the treatment of indolent lymphoid malignancies, particularly hairy cell leukemia (HCL), mycosis fungoides, and chronic lymphocytic leukemia [20]. We report the occurrence of hypersensitivity reactions in five patients treated with dCF in studies sponsored by the Division of Cancer Treatment (DCT), National Cancer Institute (NCI). Although skin toxicity in the form of a rash and dryness is known to dCF, hypersensitivity reactions have not previously been associated with dCF administration.

Patients and Methods

The case reports described were reported to the Investigational Drug Branch, NCI, between March 1985 and December 1987. Four patients were treated with dCF on DCT-sponsored phase II protocols and one was treated through a special-exception protocol. The data summarized result from complete toxicity reports by the investigating physicians. A sixth case of hypersensitivity was reported during this period; however, this case was excluded from analysis due to confounding factors such as herpes simplex (commonly associated with erythema multiforme) and possible insulin hypersensitivity. In addition, four other cases of generalized skin rashes associated with dCF therapy were reported to the DCT during this period, but as no other signs or symptoms of hypersensitivity were involved, these cases were excluded from this analysis.

Results

The demographic characteristics of the patients and the features of their reactions are shown in Table 1. Three patients had HCL, one had Sezary syndrome, and one had renal cell adenocarcinoma; their ages ranged from 39 to 71 years. All three HCL patients had experienced milder versions of the hypersensitivity symptoms on a prior dose of dCF, but only one experienced these milder symptoms on the first dose. The patient with renal cell cancer developed fatal vasculitis after receiving one dose.

The first four reactions (cases 1–4, Table 1) have many similar characteristics. Symptoms of these reactions began 2–9 days after drug administration; their clinical features included an erythematous rash distributed over the trunk and extremities, with varying degrees of itching. Rapid resolution occurred with antihistamines and/or steroids. Fever was noted in three of the patients and extensive edema in two. Eosinophilia was documented in two patients and was associated with respiratory symptoms in another.

The most serious reaction in these four patients required hospitalization and occurred in the patient with Sezary syndrome. This patient was receiving dexamethasone, allopurinol, and triamcinolone concurrently. The symptoms, which peaked 10 days after the initiation of a 3-day course of dCF, included fever, chills, cough, and severe diffuse erythema of the skin, with edema of the lower legs. There was some skin desquamation on the hands and back. No infection could be documented, and the patient's fever subsided along with the skin reaction over the next several days.

Three of these four patients were rechallenged with the drug. The reactions recurred in all three, including the patient with Sezary syndrome, who developed erythema and edema several days after treatment, in spite of the discontinuation of dexamethasone, allopurinol, and triamcinolone for the rechallenge attempt. It is noteworthy that at least two of these patients were responding to dCF at the time of their reactions; both required the termination of treatment due to this toxicity.

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Table 1. Characteristics of patients and reactions

Case* no.	Disease	Age/ sex	Cumulative dose dCF (mg/m^2)	No. of doses at onset	Reaction onset	Rash	Pruritis	Fever	Flushing	Edema	Eosinophilia	Respiratory	Hypotension	Rechallenge
1	HCL	71/M	27.5	6	2 d	+	−	+	+	+[a]	−	−[b]	−	Unknown
2	HCL	59/F	16	4	5 d	+	+	−	−	+	+	−	−	Recurred
3	HCL	39/M	10	3	3 d	+	+	+	−	−	+	−	−	Recurred
4	Sezary	64/F	40	8	9 d	+	+	+	−	+	−[c]	+	−	Recurred
5	Renal cell	70/M	4	1	7 d	−	−	+	−	+	+	−	+	NA (expired)

* Concurrent medications included: No. 1 – allopurinol and thiazide; No. 2 – diphenhydramine, vitamin D, and calcium; No. 3 – allopurinol, dexamethasone, and triamcinolone; No. 4 – unknown; No. 5 – allopurinol, furosemide, digoxin, dipyridamole, and propranolol

[a] Edema was limited to the periorbital area and the patient had conjunctivitis

[b] The patient experienced shortnessof breath on a previous dose

[c] Eosinophilia was not documented, but respiratory symptoms included cough and infiltrates

Patient 5 (Table 1) represents a more complicated and severe picture of hypersensitivity. This patient died 3.5 weeks after receiving only one dose of dCF along with allopurinol, having developed a fever 7 days after dCF. The patient was admitted on day 10 with fever, hypotension, and decreased urinary output. Autopsy revealed an inflammatory process involving arteries and veins in the heart, spleen, and cerebral cortex, consistent with hypersensitivity vasculitis.

Discussion

Hypersensitivity reactions are unusual but significant complications of cytotoxic drug therapy [26, 27]. The importance of these reactions may be substantial if the drug producing them plays a central role in the effective therapy of the disease in question. In the case of HCL, dCF may be the most effective single agent available, with response rates approaching 90% [2–4, 10, 11, 23, 24]. Complete remissions of this disease are long lasting and do not require maintenance therapy. As a result of these observations, dCF is also being studied in other lymphoid malignancies [17]. Based on the number of patients treated with dCF, we estimate the incidence of hypersensitivity reactions to be between 0.5% and 1.0%.

Skin toxicity after dCF administration has been observed in patients with several lymphoid malignancies. Although unusual in patients with cutaneous T-cell lymphoma [7] and acute lymphocytic leukemia (ALL) [21], skin reactions are frequently reported among dCF-treated patients with HCL [3, 4, 10, 11, 24]. This toxicity is characterized by a rash or dryness on the chest and limbs, especially in areas previously exposed to the sun. Concomitant medications such as allopurinol or antibiotics have been implicated in the skin reactions seen with dCF in some patients with HCL [10].

Some patients also experienced systemic symptoms such as edema, eosinophilia, and fever. The fact that three of the five patients described were under treatment for HCL is of particular interest: patients with this disease appear to have an increased incidence of drug reactions, and, in addition, skin manifestations such as erythema nodosum and perivasculitic lesions are common complications of the leukemia itself [5, 13, 22, 28].

With some hypersensitivity reactions, it is not clear whether the patient is allergic to the drug or to the vehicle in which it is formulated. dCF is preservative-free, being formulated only with mannitol and sodium hydroxide [16]; thus, it would seem that dCF itself is more likely to be the allergen. Vigorous hydration is required prior to dCF administration. At various institutions, concomitant allopurinol is routinely given with chemotherapy to patients with lymphoid malignancies to prevent hyperuricemia secondary to tumor lysis. At least three of the five patients in this report were receiving concurrent allopurinol during dCF therapy. Allopurinol has been well characterized for inducing a syndrome of skin rash, fever, hepatic dysfunction, eosinophilia, and worsening renal function [1, 8, 9, 12, 14, 15, 25, 30, 31]. Numerous cases of hypersensitivity vasculitis have also been directly attributable to allopurinol administration. It has been suggested that the use of allopurinol in combination with dCF, at least in patients with HCL, may result in enhanced toxicity [6]. Allopurinol may not be necessary after the initial few cycles of dCF in patients with bulky disease and should probably be avoided in nonlymphoid diseases. Studies of the possible interaction of dCF and allopurinol are indicated.

dCF has an unique role in several neoplasms. Further investigations of methods to overcome the effects of hypersensitivity reactions are warranted.

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