Bleomycin-induced hyperpigmentation and hypersensitivity reactions to etoposide and vinblastine in a child with endodermal sinus tumor

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We report a pediatric case who developed bleomycin-induced hyperpigmentation and hypersensitivity reactions to both etoposide and vinblastine while receiving chemotherapy for germ cell tumor. Skin hyperpigmentation related to chemotherapeutic agents has been reported only rarely in pediatric patients. This patient developed a characteristic skin hyperpigmentation which was "flagellate" in appearance. Two features of the hyperpigmentation were noteworthy: development at a low cumulative dose of bleomycin and persistence after cessation of chemotherapy. Additive effect of cisplatinum-induced hyperpigmentation was suggested. Although hypersensitivity reactions to etoposide have been previously reported, hypersensitivity reactions to vinblastine are almost unknown. To our knowledge, this is the first report of hypersensitivity reaction to vinblastine in a child in English literature.

Key words: hyperpigmentation, hypersensitivity reactions, bleomycin, etoposide, vinblastine.

Unlike some serious and life-threatening side effects of anticancer drugs, hyperpigmentation has been reported only rarely in pediatric patients because it is usually accepted as a problem of simple cosmetic concern. Hypersensitivity reaction (HSR) is another toxic side effect of anticancer therapy which may necessitate alterations in the chemotherapy regimen and may even be life-threatening. Certain drugs like L-asparaginase cause HSRs in a significant number of patients, while HSRs to some other chemotherapeutic agents like Vinca alkaloids are almost unknown[1]. An increasing number of HSRs have appeared in pediatric oncology literature, as in the case of epipodophyllotoxins, but have been noted only recently anecdotally[2].

We herein present a pediatric patient who demonstrated bleomycin-induced skin pigmentation and HSRs to both etoposide and vinblastine (VBL).

Case Report

In December 1996, a previously healthy 14-year-old girl presented with an abdominal mass, and she was diagnosed as stage IV endodermal sinus tumor originating from the left ovary with hepatic metastasis. After excision of the primary tumor, chemotherapy was started with combined PEB protocol (P: Cisplatinum 120 mg/m^2, 5 hour parenteral infusion, on day 1; E: Etoposide 100 mg/m^2 parenteral infusion over 1 hour on days 1-3; B: Bleomycin 15 mg/m^2 IV, on day 2).

During the first course of chemotherapy, a HSR developed with urticaria, flushing, bronhcospasm, cyanosis and dyspnea at the 15th minute of the first etoposide dose. The infusion was discontinued and the reaction was controlled with parenteral antihistaminic and corticosteroid. Her past history revealed no record of asthma, atopy, drug allergy or adverse reactions to radiological contrast media. Since VBL is another active agent against germ cell tumors, etoposide was replaced with VBL (6 mg/m^2 IV days 2 and 3). She tolerated the next two courses of chemotherapy well without any significant toxicity.

Three weeks after the third course, when she had already received a total of 60 mg bleomycin and 576 mg CDDP, she was noted to have areas of linear, dark brown hyperpigmentation over

the neck, inner thighs and anterior chest wall (Fig. 1). The skin lesions were not pruritic. On the fourth course, during intravenous administration of VBL, a generalized cutaneous rash developed at the 3rd minute of injection in the form of erythematous macules and urticarial plaques which were pruritic. These lesions showed a rapid resolution process after intravenous diphenhydramine and prednisolone. Two more chemotherapy courses including CDDP, VBL and bleomycin were administered with premedication (dexamethasone and diphenhydramine) in an attempt to prevent HSRs. No further HSR was observed.

Fig. 1. Close-up of linear dark brown hyperpigmentation on the inner thigh.

Renal and hepatic functions, which were monitored before each course, remained intact. Dark brown linear hyperpigmented skin lesions were mostly prominent just after the chemotherapy courses. Their color changed to light brown after the first week of chemotherapy, but never disappeared. Six courses of chemotherapy were completed in May 1997 and she has been in complete remission without any late toxic side effects since July 1999. The linear hyperpigmentation of the skin did not disappear, but got lighter during the follow-up.

Discussion

The major toxicity of bleomycin is dose-related pulmonary toxicity, which has been well established, but skin hyperpigmentation, another dose-related toxicity, has come to attention only infrequently because it causes only cosmetic trouble. Our patient developed skin hyperpigmentation in the form of fine, linear streaking over the neck, chest wall and inner thighs. This type of skin hyperpigmentation, which is "flagellate" in appearance and scattered mainly over the chest wall, is unique to bleomycin[3-5]. So for this case, hyperpigmentation was thought to be mainly related to the skin toxicity of bleomycin. Bleomycin-related skin toxicity is dose related and usually develops after a cumulative dose of 90-285 mg[3]. We observed this side effect at a lower dose (60 mg) level. Concomitantly administered CDDP may play an additive role in the early development of hyperpigmentation. Localized hyperpigmentation induced by pressure related to CDDP has been reported more recently[6]. There was no pressure effect to induce hyperpigmentation for this case, so CDDP probably played only an additional role. The exact pathogenetic mechanism for bleomycin and CDDP-induced hyperpigmentation is still not known Bleomycin-related hyperpigmentation is a reversible toxicity after the drug is discontinued, but CDDP-induced cases seems to be permanent[3,6]. The permanent hyperpigmentation in this patient may also suggest an additional role of CDDP.

Hypersensitivity reactions to two different agents developed in this patient whose past and family histories were unremarkable for allergic reactions. A severe HSR was observed at the 15th minute of the first etoposide dose, so non-immunologic mechanism was suspected. At the time, she was receiving one-hour infusion of etoposide in saline, with an etoposide concentration of less than 0.5 mg/ml; therefore, a reaction related to rapid infection was unlikely. Although the exact mechanism of HSR to etoposide is not known, it is believed to be of non-immunogenic origin since many of these reactions occur during the first exposure[7]. However, some cases suggested an immunologic base for HSRs to etoposide[8]. Although previous isolated reports seemed to establish etoposide HSRs as an uncommon event, HSRs were observed in 33 percent of pediatric patients with acute lymphoblastic leukemia in a recent study, However, only 14 percent of the reactions were grade 3[2]. The parenteral formulation of etoposide used for this case contained polysorbate 80 and benzyl alcohol, but no studies have been performed to determine whether these substances are to blame in some HSRs.

The deicision to stop or continue with the same agent after development of a HSR depends on the nature and severity of the reaction, the type of cancer that is treated and the availability of a suitable analog or another drug in the same

chemical class. Because of a grade 3 reaction, we replaced etoposide with VBL.

Most antitumor agents have been recognized to cause HSRs in at least a few cases, but HSRs to Vinca alkaloids are almost unknown[1]. Young et al.[10] reported a patient who developed HSR to VBL during a phase I study. To our knowledge, this is the first pediatric patient who developed HSR to VBL.

More data on uncommon toxic side effects of chemotherapy should appear in pediatric oncology literature to help clinicians be aware of the potential side effects and to prevent unnecessary interventions. This may also stimulate studies searching for the pathogenesis of some uncommonly occurring toxic side effects. Future prospective studies on bleomycin-induced hyperpigmentation, especially at lower cumulative doses and during the acute stages of toxicity, may help to clarify the pathogenetic mechanism for this unique toxicity.

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