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Clinical study

Cutaneous ulcers associated with hydroxyurea therapy

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Abstract Hydroxyurea is an antitumoral drug mainly used in the treatment of Philadelphia chromosome-negative myeloproliferative syndromes and sickle-cell disease. Ulcers represent a rare but severe long-term adverse effect of hydroxyurea therapy.

Hydroxyurea-induced ulcers are often multiple and bilateral, typically developing in the perimalleolar region, although any cutaneous district is potentially affected. They generally look small, well-defined, shallow with an adherent, yellow, fibrinous necrotic base. A constant finding is also an extremely intense, treatment-resistant pain accompanying these ulcerations. Withdrawal of the drug generally leads to spontaneous healing of these lesions.

Care providers tend to show insufficient awareness of this highly debilitating cutaneous side effect, and late or missed diagnoses are frequent. Instead, regular dermatologic screening should be performed on hydroxyurea-treated patients.

This article will present a comprehensive review of indexed case reports and clinical studies, followed by a discussion about treatment options aiming at increasing knowledge about this specific topic.

Introduction

Cutaneous ulcers represent a pathology typical of the lower limb, due to the anatomy of its terminal circulation, and are usually caused by arterial insufficiency, venous stasis or metabolic diseases such as diabetes. Ulcers are common as well in myeloproliferative disorders (MPDs) and in sickle

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cell disease (SCD), due to the alteration of microcirculation typical in these conditions [1]. Also drugs, including hydroxyurea (HU), can be a rare cause of ulcers [2].

Hydroxyurea pharmacological properties and mechanisms of action

HU or hydroxycarbamide, firstly synthesized in 1869 by Dresler and Stein from hydroxylamine and hydrogen cyanate [3,4], is a non-alkylating hydroxylated urea analog with antineoplastic and antiviral properties [5]. It is indicated in the treatment of Philadelphia-chromosome negative myeloproliferative syndromes (MPs), sickle cell disease (SCD), psoriasis [6], some solid cancers and it was proposed in combination with antiretroviral drugs in the therapy of HIV infection [7].

HU is an easily absorbed drug and reaches peak blood levels 1—2 h after ingestion. It has an almost complete bioavailability and distributes in the water compartments of the body so that intravenous administration is usually unnecessary. It can cross the blood—brain barrier and the placenta, and can be found in breast milk. It is eliminated mainly through the kidneys [5].

HU was a pioneer drug in the treatment of solid cancer, but unlike the other first generation-chemotherapeutics is not a metabolite analog; it is instead a non-competitive inhibitor of the enzyme ribonucleotide reductase (RR), which is essential for the synthesis of deoxyribonucleotides from ribonucleotides. Inhibition of RR results in depletion of desoxyribonucleotides (dNTPs), cessation of DNA synthesis and death of S-phase cells. Moreover, HU can bind and inhibit another enzyme, histone deacetilase, thus inducing differentiation of tumoral cells via c-jun expression [8]. Also, HU induces sensitization of tumors to other chemotherapeutic agents through a yet different mechanism: the depletion of dNTPs facilitates the activity of pyrimidine and purine antimetabolites; RR also plays a role in DNA repair, therefore HU is associated with dsDNA breaks; HU could possibly help reverse acquired tumoral resistance to chemotherapy promoting loss of extrachromosomal-amplified genes [5].

Hydroxyurea systemic and dermatological side effects

Despite its reputation of being a safe drug, the reported adverse events during HU treatment are numerous and concerning different body systems; not surprisingly, tissues with high cell turnover are the most affected by the cytostatic action of HU.

HU can affect bone marrow causing myelosuppression, bleeding and, rarely, leukemic transformation. B12 or folate-unrelated macrocytosis can occur. Oral mucosal ulcerations and pigmentation, accompanied by nausea and vomiting, epigastric pain and diarrhea represent the most common reported gastrointestinal side effect of HU therapy [5—9]. Ulcers of genital mucosa have also been described [10,11]. High fever outbreak sometimes associated with maculopapular rash and abnormal liver function tests [12], pneumonitis and bronchiolitis obliterans [13], vasculitis [14] and gangrene in toes [15,16] have also been reported in literature as HU possible adverse effects.

HU therapy has been associated with multiple cutaneous alterations (Table 1) such as xerosis, scaling, atrophy of the skin and subcutaneous tissues, skin hyperpigmentation, facial and acral erythema, palmoplantar keratoderma, solar hypersensitivity with eruptive appearance of squamous cell and basal cell carcinomas on sun-exposed sites, partial non-cicatricial alopecia, nail alterations and cutaneous ulcers (Fig. 1a,b) [17].

To this range of cutaneous complications should also be added a characteristic eruption, unique to patients affected by hematologic malignancies, described in the literature through multiple names: lichen planus-like lesions [18,19], dermatomyositis-like lesions, pseudo-dermatomyositis, Gottron-like papules, dermatomyositis without myositis [20—23] as well as being associated with graft-versus-host disease [24]. Daoud proposed recently the definition of hydroxyurea dermopathy for this unique nosological entity [25]. It is characterized by a poikilodermatous eruption with telangiectasia, erythema, scaling, and lichenoid papules resembling Gottron's papules of dermatomyositis, usually on the dorsa of hands and knuckles.

HU-induced non-melanoma skin cancer usually occurs in clear Fitzpatrick phototype-patients

Table 1 Mucocutaneous side effects of hydroxyurea.

1. Skin atrophy, xerosis cutis, and acquired ichthyosis
2. Facial and acral erythema
3. Palmoplantar keratoderma
4. Alopecia
5. Cutaneous and mucosal hyperpigmentation
6. Dermatomyositis-like eruptions
7. Onychodystrophy, and melanonychia
8. Actinic keratoses and squamous cell carcinomas
9. Cutaneous and mucosal ulcers