CASE REPORT

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Hydroxyurea and nonmelanoma skin cancers: report on three cases and review of the literature

Hidroksiurea i nemelanomski karcinomi kože: prikaz tri bolesnika i pregled litrature

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Abstract

Introduction. Hydroxyurea (HU) is a cytostatic agent, frequently used for the treatment of myeloproliferative disorders, sickle cell anemia and severe forms of psoriasis. Cutaneous side effects occur in up to one third of patients taking hydroxyurea, with the most serious side effect being susceptibility to develop non-melanoma skin cancers. **Case report.** We report 3 patients using HU that have developed multiple skin malignancies on the head and neck region and dorsa of the hands, arranged according to the level of the overall squamous dysplasia expressed. **Conclusion.** A cumulative dose of hydroxyurea affects skin cancer promotion in concordance with other risk factors determining cumulative ultraviolet exposure (age of the patients, skin phototype, sun habits), but the exact influence of each of them and enrollment of other possible cofactors remains to be elucidated. We point out the importance of adequate skin cancer preventive and therapeutic approach to the patients treated with hydroxyurea.

Key words:
skin neoplasms; ultraviolet rays; hydroxyurea; treatment outcome.

Apstrakt

Uvod. Hidroksiurea je citostatik koji se često koristi u terapiji mijeloproliferativnih oboljenja, anemije srpastih ćelija i težih oblika psorijaze. Neželjena dejstva na koži manifestuju se u oko trećine bolesnika lečenih hidroksiureom, među kojima je najozbiljnije neželjeno dejstvo sklonost pojavi nemelanomskih karcinoma kože. **Prikaz bolesnika.** U radu su prikazana tri bolesnika lečena hidroksiureom kod kojih je došlo do razvoja brojnih maligniteta kože u predelu glave, vrata i dorzuma šaka, redosledom prema nivou ukupne prisutne skvamozne displazije. **Zaključak.** Kumulativna doza hidroksiuree utiče na nastanak karcinoma kože u sadejstvu sa drugima faktorima rizika koji određuju kumulativnu izloženost ultraljubičastom zračenju (životno doba, fototip kože, obrazac izlaganja suncu), ali precizniji uticaj svakog od navedenih, kao i uticaj mogućih drugih kofaktora tek treba razjasniti. Ističemo važnost adekvatne prevencije i terapije karcinoma kože kod bolesnika lečenih hidroksiureom.

Ključne reči:
koža, neoplazme; ultravioletni zraci; hidroksiurea; lečenje, ishod.

Introduction

Hydroxyurea (HU) is a cytostatic agent that inhibits cellular DNA synthesis. Due to its high therapeutic efficiency and manageable dose-related toxicity, HU is frequently used for the treatment of myeloproliferative disorders, sickle cell anemia and severe forms of psoriasis [1, 2]. In up to one third of patients taking HU a wide variety of cutaneous side effects occur: dryness and scaling, hyperpigmentation of skin and nails, partial non-scarring alopecia, skin atrophy, skin and mucosal ulcerations, facial and acral erythema, palmoplantar keratoderma, lichenoid and dermatomyositis-like eruption (DMLE) [3, 4]. It has been observed that HU contributes to photo damage of sun exposed skin areas, primarily the head and neck region and dorsa of the hands, inducing skin changes described as "HU-associated squamous dysplasia" (HUSD) [5] and promoting development of non-melanoma skin cancers (NMSC), namely actinic keratoses (AK), keratoacanthomas (KA), squamous cell carcinomas (SCC) and basal cell carcinomas (BCC).

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Case report

We reported three patients using HU as a single specific therapy that developed multiple skin malignancies on the head and neck region and dorsa of the hands, arranged according to the level of the overall squamous dysplasia expressed (Figures 1, 2 and 3). Two patients suffered from *polycythemia rubra* vera (PRV) where HU is usually prescribed in lower doses, and one patient from chronic granulocytic leukemia (CGL) periodically taking up to 3 g of HU daily. All three patients were Caucasian, males, non-smokers, denied alcohol abuse, with family history negative for skin cancers. All were long-term occupationally sun exposed and had no sun protection habits. Other significant data are presented in Table 1. For flat lesions with AK features dignosis was made by dermoscopy and they were treated mainly by conservative options, while all nodular and/or hyperkeratotic lesions were biopsized or excised. Apart from anticancer treatment performed, presented in Table 1, all three patients were advised of meticulous sun protection.

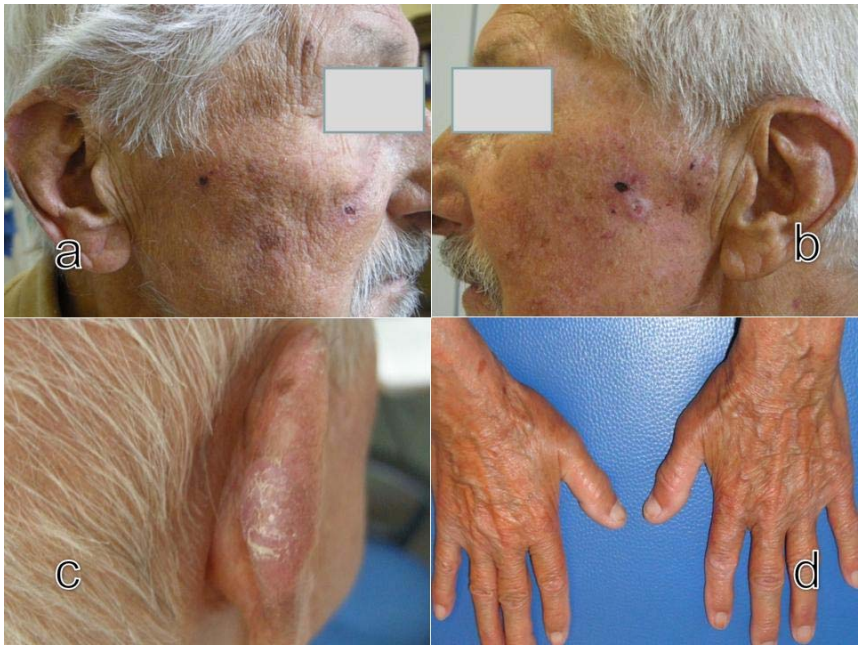

Fig. 1 – Fotoexposed skin areas in the patient 1: a) basal cell carcinoma (BCC) and multiple acinic keratoses (AK) on the right cheek; b) squamous cell carcinoma (SCC) and multiple AK on the left cheek; c) SCC on the right helix; d) clinically intact skin of the dorsa of the hands.

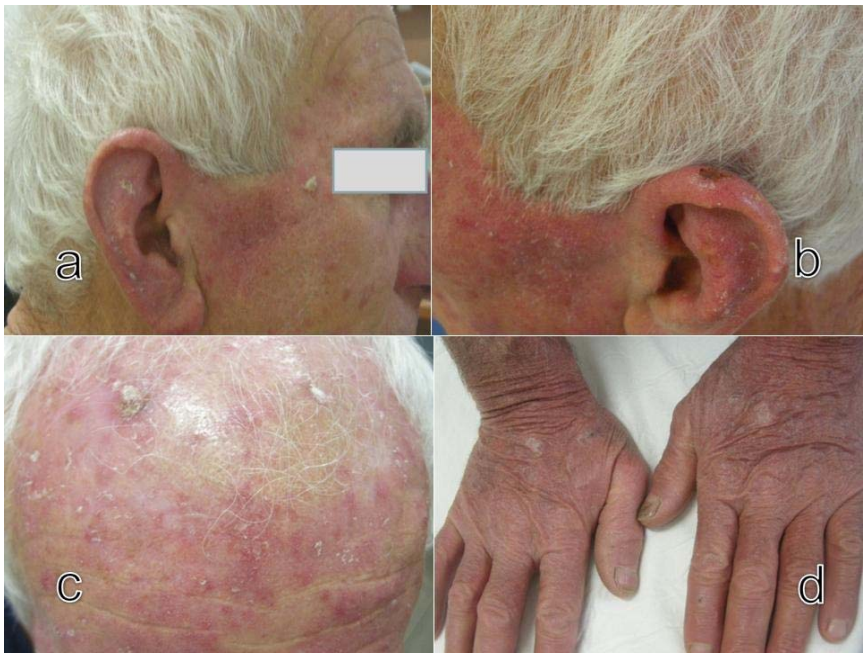

Fig. 2 – Fotoexposed skin areas in the patient 2 – multiple actinic keratoses (AK): a) on the right cheek; b) on the left cheek; c) multiple squamous cell carcinoma (SCC) *in situ* on the frontoparietal region; d) on the dorsa of the hands.

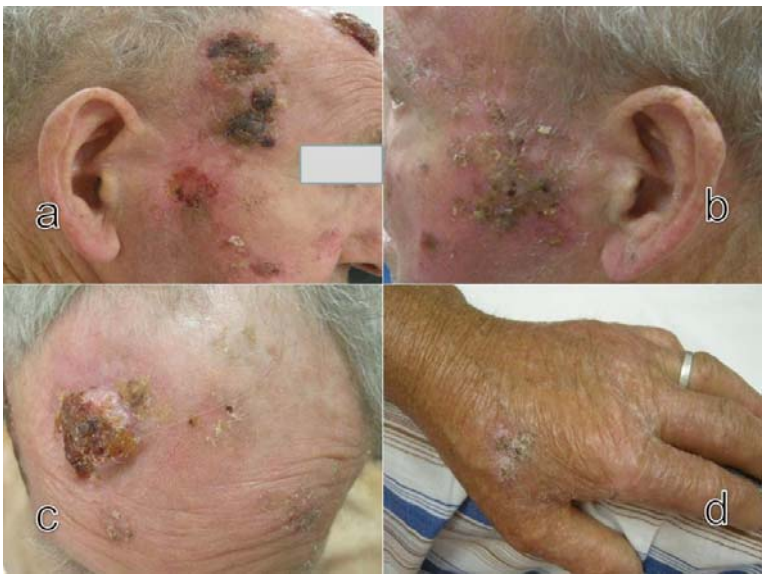

Fig. 3 – Fotoexposed skin areas in the patient 3 – multiple actinic keratoses (AK) and multiple invasive squamous cell carcinoma (SCC): a) on the right temporal and preauricular region; b) on the left preauricular region; c) on the frontoparietal region; d) on the dorsa of the hands.

Table 1

Additional relevant features of reported patients

Features	Case 1 (Figure 1)	Case 2 (Figure 2)	Case 3 (Figure 3)
Age (years)	82	72	73
Skin phototype*	III	II	II
Sunburns in childhood or adulthood	No	Yes, both	Unreliable
Hematological disorders	PRV	PRV	CGL
HU daily doses (g)	1–1.5	1–1.5	2–3
HU cumulative dose and length of therapy at the onset of the first skin malignancy	1.8 kg in 5 years	1.4 kg in 4 years	2.9 kg in 4 years
HU total dose and total length of therapy	> 2.9 kg during 8 years	> 4 kg during 11 years	> 4.3 kg during 6 years
Skin tumors during follow-up	Multiple AK 1 BCC 2 invasive SCC	Multiple AK 1 KA 1BCC 3 *in situ* SCC 1 invasive SCC	Multiple AK Multiple invasive SCC
Treatment applied	Cryosurgery, 5-FU cream, Surgical excisions	Imiquimod cream Surgical excisions Acitretin chemo-prevention	Following multiple biopsies patient refused radical surgery and was lost to follow-up

***Skin phototype according to Fitzpatrick [6]**
HU – hydroxyurea; PRV – *polycytemia rubra vera*; CGL – chronic granulocytic leukemia; AK – actinic keratose; KA – keratocanthomas; BCC – basal cell carcinoma; SCC – squamous cell carcinoma; FU – fluorouracil.

Discussion

Hydroxyurea became an antiproliferative treatment option in the 1960s [7], and is widely used ever since in coping with numerous hematological and other conditions.

HU-associated skin eruption was initially reported in 1975, described as lichen planus like eruption with histology of an interface dermatitis. In 1995 a form of HU-induced eruption with a tendency to mimic true dermatomiositis was recognized and named DMLE [3]. The first report of a potential HU influence on promoting skin cancers was given in 1991 [8], followed by multiple similar case reports [9–12], drawing attention to the most serious HU adverse effect and changing perspective on HU-induced skin lesions. The term "hydroxyurea dermopathy" was introduced in 1997, describing "focal to more extensive squamous changes of basal cell keratinocytes" [13], while in 2004 a more precise terminology proposition of HUSD was made [5]. Further research of the number and distribution of p53 mutated keratinocytes along the lower layers of the epidermis suggested that HU-associated DMLE is a premalignant state, but to a lesser degree compared to HUSD, since DMLE showed focal p53 expression in a confluent nuclear pattern, while HUSD showed diffuse p53 expression [3, 5]. Mutant p53 keratinocyte clones represent hallmark of AK and SCC [14]. The observation that DMLE lesions have a latency period of 3 to 5 years, compared to longer latency for NMSC [3], concurs with

theory that DMLE is a predecessor of HUSD, which precedes HU-NMSC, all being just different evolutionary phases.

The exact interdependence between the HU mechanism of action and neoplastic skin alterations is still not completely understood. In general, HU acts as an inhibitor of cellular DNA synthesis, through inactivation of the enzyme ribonucleotide reductase, thus leading to cell apoptosis [3].

It has been proposed that a direct cumulative damage, as well as a cytotoxic effect of HU on basal keratinocytes results in promoting skin cancers. In experimental models HU produces carcinogenic agents such as N-methyl-N-nitrosourea, induces direct chromosomal damage and inhibits DNA repair in ultraviolet (UV)-irradiated cells [15–17]. The cytotoxic effect of HU promotes atrophy of the skin that enables a higher degree of UV penetration and UV damage [3].

The results of the study [18] that examined chromosomal HU effect in the presence of metal ions show that HU causes DNA damage in the presence of copper ion Cu(II), and inhibition of DNA damage in the presence of bathocuproine, a copper ion specific chelator. No HU induced DNA damage was recorded in the presence of cobalt, nickel, manganese or iron ions. Researchers observed that characteristic oxidative DNA lesions increased with increasing concentration of hydroxyurea in the presence of Cu(II). Copper is an essential component of chromatin, but obviously has the ability to catalyze the production of reactive oxygen species to mediate oxidative DNA damage [19]. Whatever the cause (excess intake or constitutional excess), the elevated copper metal ion concentration could affect pharmacological properties of HU.

The suspected role of human papillomavirus infection as a cofactor in the development of HU-NMSC has not been proved yet [20].

An interesting evidence of HU influence reports female monozygotic twins, with only difference that lies in the fact that of 1 of them who was taking HU developed severely sun damaged skin, multiple Bowenoid AK and SCC *in situ* [21].

The true incidence of NMSC in patients taking HU is unknown. In the case series of 26 patients taking HU, 8 patients had AK and 2 of them developed SCC [4]. There are also no established criteria that can help us recognize the group of patients taking HU with higher risk of developing NMSC. Concomitant excessive UV exposure, duration of treatment and the cumulative dose of HU are recognized as important risk factors.

Like the majority of the reported cases, our patients were older subjects with mostly fair skin types, all had positive history of excessive UV exposure and no sun protection habits. NMSC are not recorded in patients taking HU for the treatment of sickle cell anemia, which is a hereditary disease affecting young black individuals [22]. On the other hand, a report of a patient developing exclusively mucosal SCC at a cumulative dose of more than 6 kg HU, with no associated risk factors for oral SCC [23], as well as a case of a 59-year-old male with multiple SCCs taking 1 g of HU per day during 6 years, with skin phototype IV and a lack of over photo exposure [1], indicate importance of other factors apart from UV exposure.

The duration of HU intake as a cofactor is well illustrated in a study reporting 158 patients receiving HU for chronic myeloid leukemia (CML), where only 5 of them developed NMSC. Patients with NMSC received HU for an average of 76 months, compared to the average of 38 months in all the other patients from the cohort [7]. NMSC are not recorded in patients taking HU for the treatment of psoriasis, and the explanation may be significantly shorter treatment courses. Our patients developed first NMSC lesions after 4 to 5 years of continuing HU therapy.

Cumulative HU dose is another important cofactor. A case series of 5 patients with NMSC reports cumulative doses varying from 0.65 to 3.6 kg HU, in average taken during 6.5 years [12]. Our patients developed first NMSC lesions at the individual cumulative dose of 1.8 kg; 1.4 kg and 2.9 kg, respectively. It is unclear whether HU intake played any role in promoting NMSC in a case report of a 74-year old female with PRV who developed just one SCC after a cumulative dose of only 0.6 kg, and no other NMSC appeared during next 6 years of follow up despite ongoing HU therapy [24].

Besides abovementioned risks, patients suffering from CML have additional burden of disease-related immunosuppression [17] which modifies tumor behavior and prognosis. The latency period is usually shorter and tumors are more aggressive [8, 16]. Some of the reported CML patients developed NMSC even years after the discontinuation of the HU therapy [9, 15, 25].

There are reports of Merkel cell carcinoma in 2 patients taking HU [26, 27], but until larger number of cases are registered, these should be considered as a coincidental association.

Marked predominance of AK-SCC spectrum compared to BCC lesions in a total body of reported cases, including our case series, could be due to a combined UV and HU influence on specific molecular pathway [28], but further investigations are needed.

The management of the patients developing NMSC while taking HU is complex and multidisciplinary approach is mandatory. Most of the HU associated NMSCs were treated by surgery, but repeated topical 5% imiquimod treatment is a good therapeutic option for well preselected lesions [9, 29] and chemoprevention with retinoids is a possible viable tool. Close collaboration between general practitioner, hematologist, dermatologist, oncologist and reconstructive and/or maxillofacial surgeon is mandatory.

Conclusion

Our findings indicate that a cumulative dose of HU affects skin cancer promotion in concordance with other risk factors determining cumulative UV exposure (age of the patients, skin phototype, sun habits). The level of HU and possible cofactor influence remains to be elucidated, since the case-control studies are still lacking.

Nevertheless, it is important to recognize the higher risk for development of NMSC in patients taking HU, to take preventive measures through educating patients in photo protection and self-examination of the skin, to organize periodic preventive thorough skin examinations by professionals and to discontinue or replace HU therapy at the onset of the first NMSC, if possible.

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