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Precancerous skin lesions and malignant skin tumors associated with hydroxyurea treatment: Evaluation of a large series and review of the literature

Hidroksiüre tedavisi ile ilişkili prekanseröz deri lezyonları ve malign deri tümörleri: Geniş bir serinin değerlendirilmesi ve literatürün gözden geçirilmesi

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Abstract

Background and Design: Malignant skin tumors have been reported in patients using hydroxyurea (HU) for hematological disorders. This study aimed to investigate the characteristics of precancerous skin lesions and malignant skin tumors in association with long-term HU therapy.
Materials and Methods: Records of consecutive patients diagnosed with precancerous and cancerous skin lesions during HU therapy in a single dermatology department between 2008 and 2021 were retrospectively analyzed.
Results: Among 13 patients (mean age: 66.5 years) treated with HU for five different hematological diseases, 11 had used HU >5 years, whereas the time was shorter in the other two patients. The period between HU treatment initiation and the appearance of the first lesion was approximately 9-10 years. Actinic keratosis (AKs) were found in two patients, non-melanoma skin cancers (NMSCs) accompanied by AKs in seven patients, and only NMSCs in four patients. Melanoma was seen in a patient with NMSCs and AKs. In total, 12 basal cell carcinomas (BCCs), 12 squamous cell carcinomas (SCCs), and one melanoma were diagnosed. The superficial type was the most common type of BCCs, followed by the nodular type. NMSCs were located mainly on the face, followed by the scalp, neck, and extensor surfaces of the upper extremities.
Conclusion: The results of this large series support the possibility of the relationship between UV-induced skin cancer and HU therapy. SCCs and BCCs showed equal incidence in the present study in contrast to some previous reports, and different BCC types may occur in these patients. As many patients have more than one malignant skin tumor, protective measures against sunlight, which is another inducing factor for these tumors, and a long-term follow-up, should not be ignored.
Keywords: Hydroxyurea, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, melanoma

Öz

Amaç: Hematolojik hastalıklar için hidroksiüre (HÜ) kullanan hastalarda malign deri tümörü gelişimi daha önce bildirilmiştir. Bu çalışma ile uzun süreli HÜ kullanımı ile ilişkili premalign deri lezyonları ve malign deri tümörlerinin tüm özelliklerinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: Tek bir dermatoloji merkezinde 2008-2021 yılları arasında HÜ tedavisi sırasında prekanseröz deri lezyonu veya malign deri tümörü tanısı alan ardışık hastaların dosyaları retrospektif olarak incelendi.
Bulgular: Beş farklı hematolojik endikasyon için HÜ kullanan 13 hastada (ortalama yaş 66,5 yıl) prekanseröz deri lezyonu [aktinik keratoz (AK)] veya malign deri tümörü görüldü. Hastalardan 11'i bu ilacı 5 yıldan uzun süre kullanmışken 2'sinde bu süre daha kısaydı. İlk lezyonların oluşumu ile ilacın başlangıç tarihi arasında ortalama 9-10 yıllık bir süre vardı. İki hastada tek başına AK görülürken 7 hastada melanom dışı deri kanseri ve AK beraber görüldü. Dört hastada ise sadece melanom dışı deri kanseri saptandı. Melanom dışı deri kanseri ve AK görülen hastaların birinde ayrıca melanom saptandı. Toplamda 12 bazal hücreli karsinom (BHK), 12 skuamöz hücreli karsinom (SHK) ve 1 adet melanom tanısı

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konuldu. En sık görülen BHK tipi, yüzeyel tipti ve bunu nodüler tip takip etti. Melanom dışı deri kanserlerinin en sık yerleştiği bölge yüz olup bunu saçlı deri, boyun ve üst ekstremite ekstansör yüzeyleri izledi.
Sonuç: Bu geniş serinin sonuçları, UV ilişkili deri maligniteleri ve HÜ tedavisi ilişkisi olasılığını güçlendirmektedir. Daha önceki bazı yayınlardan farklı olarak SHK ve BHK aynı insidansta görülmüş, BHK'nin farklı tiplerine rastlanabileceği saptanmıştır. Birçok hastada birden fazla malign deri tümörü olduğu göz önünde bulundurulduğunda HÜ tedavisi alan tüm hastalarda bu tümörlerin oluşumunu kolaylaştıran diğer bir faktör olan güneş ışığına karşı koruyucu önlemlere uyulmasının sağlanmasının ve uzun dönem takibin ihmal edilmemesinin önemi ortaya çıkmaktadır.
Anahtar Kelimeler: Hidroksiüre, aktinik keratoz, bazal hücreli karsinom, skuamöz hücreli karsinom, melanom

Introduction

Hydroxyurea (HU), a ribonucleotide reductase inhibitor, has been commonly used for the long-term treatment of various hematological disorders[1-5]. Its mucocutaneous side effects vary widely from benign conditions including alopecia, xerosis, hyperpigmentation, acral erythema, dermatomyositis-like eruption, leukocytoclastic vasculitis, atrophy, keratoderma, and leg ulcers to precancerous skin lesions and skin cancers[6-10]. Squamous dysplasia, actinic keratosis (AK), Bowen's disease, keratoacanthoma, squamous cell carcinomas (SCC), basal cell carcinoma (BCC), and Merkel cell carcinoma have been occasionally reported during or after the long-term treatments with HU, mostly used for myeloproliferative disorders[7-10]. However, their real incidence and further clinical features in association with HU therapy have not been well described yet. This study aimed to investigate precancerous skin lesions and types of malignant skin tumors that occurred under HU therapy including their detailed clinical features in a relatively large series. The relevant literature was also reviewed, and findings were compared with the results of this series.

Materials and Methods

This retrospective cross-sectional study was performed in a single dermatology department enrolled consecutive patients who were diagnosed with precancerous skin lesions and malignant skin tumors during or following HU treatment for hematological disorders between 2008 and 2021. Data of these patients including follow-up data were retrospectively reviewed, and demographic features of the patients (age and sex), primary hematological disease, duration of HU treatment, and other cytoreductive therapies were recorded.

Ethical approval was obtained from the İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee (approval number: 12, date: 11.06.2021). Diagnoses of all malignant skin tumors were confirmed by histopathological examination but diagnoses of AKs were established based on clinical and/or histopathological evaluation.

Statistical Analysis

The descriptive statistics were given as means ± standard deviations (minimum-maximum). Furthermore, types, subtypes, and localization of precancerous skin lesions and malignant skin tumors including their chronologic relationship with HU treatment were evaluated.

Results

During the study period, 13 patients (9 men and 4 women) who were on HU or previously treated with HU because of various hematological disorders were diagnosed with precancerous and cancerous skin lesions in a single dermatology department. The epidemiological and clinical features of these patients are summarized in Table 1. The mean age of these patients was 66.5±15.39 (range: 36-85) years at the time of diagnosis of the first precancerous and/or cancerous skin lesion. The Fitzpatrick skin type of the patients varied between 2 and 3; however, in three patients, it was not recorded. The primary hematological disorders were as follows: polycythemia vera (n=7), essential thrombocythemia (n=3), thalassemia (n=1), chronic myeloid leukemia (n=1), and myelofibrosis (n=1). Three of the patients received HU monotherapy, and 10 patients received other cytoreductive drugs such as anagrelide (n=7), ruxolitinib (n=2), busulfan (n=1), and interferon (n=1). The mean duration of HU treatment until the recognition of the first precancerous or cancerous lesion was 9.7±6.97 (range: 0.4-28) years. All but two of the patients were still on HU during the diagnosis of their first skin tumor. The first skin tumor was diagnosed 3 and 4 years after the discontinuation of HU treatment in two patients (cases 13 and 9, respectively). One of these patients who were also on busulfan and ruxolitinib was treated with HU for only 5 months (case 9). The other patient (case 13) was on ruxolitinib on the first visit to the dermatology department 15 years after the HU therapy.

While AKs were seen in isolation in two patients, non-melanoma skin cancers [(NMSCs); BCC, n=2; SCC, n=4; both BCC and SCC, n=1] accompanied AKs in seven patients (Figure 1a, b). In other four patients, only NMSCs (SCC, n=1; BCC, n=1; both BCC and SCC, n=2) (Figure 1c) were seen. A total of 12 BCCs and 12 SCCs were diagnosed in 11 patients. The BCC subtypes were as follows: Superficial (n=6; Figure 1d), nodular (n=5; Figure 1e), and morphoeic (n=1; Figure 1f). The face, particularly the nose and forehead, was the area mainly involved (n=11) by NMSCs, followed by the scalp (n=1), neck (n=2), and extensor surfaces of the upper extremities (n=4) (Figure 1). In only one patient (case 1), superficial BCCs involved the trunk (Figure 1d). Patients with multiple BCCs did not present with any other signs or symptoms that might relate to Gorlin syndrome. None of the SCCs in this series were metastatic. Furthermore, an *in situ* superficial spreading melanoma and a sebaceous adenoma accompanied by other lesions occurred in one patient each.

In situ melanoma and all NMSCs, excluding some superficial BCCs, were surgically excised. Some of the superficial BCCs were treated with imiquimod topically. A mean follow-up duration of 3.2±3.25 (range: 0.5-12) years could be achieved in 11 of the patients, and two patients were lost to follow-up. In addition to two patients in whom malignant skin tumors initially developed after the cessation of HU therapy, new skin tumors (BCC, n=1; SCCs, n=2) developed in one patient despite the discontinuation of HU treatment after the diagnosis of the first skin tumor. Moreover, in two patients who had to continue HU therapy (cases 1 and 4), new BCCs (n=4) and AKs developed, respectively.

Table 1. Precancerous skin lesions and malignant skin tumors in 13 patients treated with hydroxyurea

Patient	Age, sex	Primary hematological disorder	Other cytoreductive therapy	Duration of hydroxyurea treatment before diagnosis†	Duration of lesions‡	Actinic keratoses (localization)	Associated malignant tumors (type)	Localization of malignant tumors	Follow-up duration in the dermatology department
1	38, M	Thalassemia	-	5 years	1.5 years	-	6 BCCs (4 superficial, 1 nodular and 1 morphoeic)	Shoulder, trunk, back, arm, and forehead	12 years
2	81, M	Polycythemia vera	Interferon alpha-2a	10 years	1 year	Multiple (face)	SCC	Neck	1 year
3	36, F	Essential thrombocythemia	Anagrelide	2 years	4 years	Multiple (dorsum of hands)	2 SCCs	Dorsum of hands	5 years
4	65, F	Polycythemia vera	Anagrelide	12 years	8 months	Solitary (face)	2 SCCs	Forearm, nose	4 years
5	66, M	Essential thrombocythemia	Anagrelide	5 years	N/A	Multiple (preauricular, nose§, forehead§)	-	-	3 years
6	75, M	Polycythemia vera	Anagrelide	28 years	1 year	Solitary (scalp)			1 year
7	66, M	Polycythemia vera	Anagrelide	13 years	N/A	Multiple (dorsum of the hand§)	3 SCCs BCC (nodular) sebaceous adenoma	Upper lip, neck, ear Forehead Neck	3 years
8	85, F	Essential thrombocythemia	Anagrelide	7 years	5 years	-	BCC (nodular) SCC	Nose Cheek	3 years
9¶	55, M	Chronic myelogenous leukemia	Busulfan, ruxolitinib	5 months	1 month	Multiple (face§)	SCC	Scalp	2 years
10	75, M	Polycythemia vera	-	11 years	N/A	Multiple (nose, scalp§, face§)	BCC (nodular)	Nose	10 months
11	81, M	Polycythemia vera	-	10 years	3 months	Solitary (nose)	BCC (nodular)	Nose	N/A
12	74, M	Polycythemia vera	Anagrelide	7.5 years	1 month	-	SCC	Cheek	N/A
13	67, F	Myelofibrosis	Ruxolitinib	15 years	N/A	-	2 BCCs (2 superficial) SCC	Nose Nose	6 months

†Initial onset of the precancerous skin lesions and/or malignant skin tumors, ‡Between the initial onset of the first precancerous skin lesion and/or malignant skin tumor and diagnosis due to of the patient history, §Diagnosis was established only by clinical evaluation, ¶After 2 years of HU cessation, *in situ* melanoma was excised on the trunk. F: Female; M: Male; N/A: Not available, BCC: Basal cell carcinomas, SCC: Squamous cell carcinomas, HU: Hydroxyurea

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Discussion

Although the relationship between HU and malignant skin tumors was previously shown in other studies mainly based on reports of hematology clinics, the current dermatology center-based study reporting malignant skin tumors or precancerous skin lesions presents a detailed description of clinical features. In the study period, a total of 4,121 patients were diagnosed with AK, Bowen's disease, SCCs, or BCCs in our dermatopathology department (unpublished data) and HU-induced cases (n=13) accounted a small percentage (0.3%) of the total group.

Besides HU, certain medications may also lead to the development of skin cancers through different mechanisms. The induction of secondary keratoacanthoma and SCC under vemurafenib or dabrafenib treatment, which is primarily used for BRAFV600-mutant metastatic melanoma, is another well-known example of this phenomenon[11,12]. Furthermore, the risk of the development of secondary malignancies, especially skin cancers, appears to be increased in patients with myeloproliferative neoplasia[13,14]. However, whether this higher risk is caused by the cytoreductive drugs or immune dysregulation associated with myeloproliferative neoplasia remains unclear[15]. In a study with a large series evaluating risk factors for NMSC development in patients with myeloproliferative neoplasms, exposure to cytoreductive drugs such as busulfan (alkylating agent) or high cumulated doses of HU were found to be independent risk factors[16]. Furthermore, the increased risk of NMSCs was also observed in patients with myeloproliferative neoplasms using pipobroman (alkylating agent) and ruxolitinib (JAK inhibitor)[13,17-20]. In one large study, duration of HU therapy and ruxolitinib therapies of >5 years was found as a risk factor for NMSCs in patients with myelofibrosis treated with ruxolitinib[19]. However, other studies have stated that some patients with NMSCs treated with ruxolitinib therapy were also exposed to HU previously[21,22]. In general, a relationship exists between long-term HU therapy and development of precancerous and cancerous skin lesions[7-10]. Among the 13 patients who received HU therapy, two used busulfan and/or ruxolitinib after HU treatment in the present series. One of them was still on ruxolitinib treatment at the first visit, whereas the other had used HU for 5 months before busulfan and ruxolitinib. This combination of HU and other cytoreductive drugs in the treatment of two patients of the present series made it difficult to evaluate the role of HU alone in the development of skin cancers and leads to the question of whether both drugs had an additional triggering effect on NMSCs in these patients.

Because of insufficient data in the present study, it is impossible to interpret the relationship between NMSCs and daily or cumulative dosage of HU. On the contrary, the male predominance in the present series was found to be in line with a previous report, indicating male sex as a risk factor for NMSCs in patients with essential thrombocythemia and polycythemia vera[16].

Besides its role in the long-term treatment of hematological disorders as an anti-metabolite by locking down the DNA synthesis and cell cycle at G1/S[23], HU may also induce a damaged repair of DNA that sensitizes keratinocytes against UV radiation, resulting in the progression of p53-mutated keratinocyte clones to squamous dysplasia, particularly on the sun-exposed areas of the body. Thus, HU and UV may synergistically

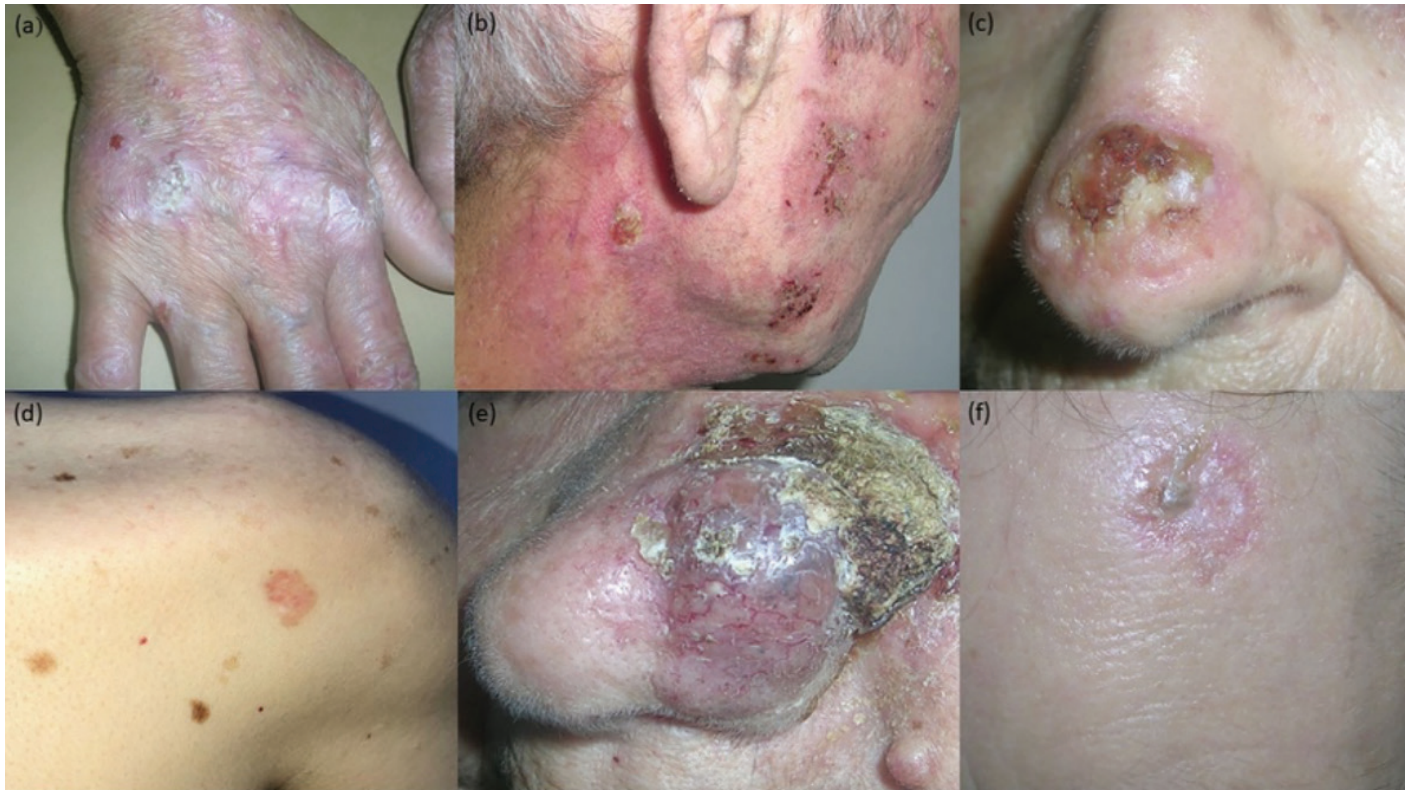

Figure 1. SCC on the dorsum of the hand surrounded by multiple actinic keratoses (a). SCC on the neck accompanying multiple actinic keratoses on the face (b). SCC on the nose (c). Superficial BCC on the shoulder (d). Nodular BCC on the nose (e). Morphoeic BCC on the forehead (f)

SCC: Squamous cell carcinomas, BCC: Basal cell carcinomas

elicit cutaneous precancerous and cancerous lesions after a latent period. Although sun exposure data of the study patients during their HU treatment were lacking, having skin phototypes 2 and 3 in the majority of these patients can be considered a relative risk factor for NMSC development. In support, all but two NMSCs in the present series involved the sun-exposed areas of the body including the face, particularly the nose, forehead, scalp, neck, and upper extremities.

In the present series, the patients were treated with HU because of five different hematological indications. Therefore, underlying hematological diseases do not appear to be related to the development of skin tumors. Although the causality between the development of skin cancer and HU does not appear to be absolute, findings in the present series including the co-existence of different types of skin tumors in three patients, presence of multiple lesions of NMSCs, abrupt onset of some lesions after HU administration, absence of previous skin cancer history, and termination of the occurrence of new skin tumors after HU cessation in most patients indicate a causal role of HU, which was also pointed out previously by Sanchez-Palacios and Guitart[8].

Among precancerous skin lesions, multiple AKs are the most common problems in patients on HU therapy, as it were in six patients of the present series[24,25]. Additionally, three patients had solitary AK. Bowen disease[7,26] and keratoacanthomas[24,27] were reported as other HU-associated precancerous skin lesions or low-grade tumors in the literature, but none of the patients presented with these types of skin lesions in the present series.

Of the 13 patients in this series, 11 have used HU for >5 years. The duration from HU initiation to the initial onset of NMSCs was reported as an average of 6.55 years in the literature[10] and 6.25 years (range: 1-204 months) in another review[28], but it was 9.7 years in the present series. Furthermore, the shortest duration from HU treatment initiation until the onset of skin lesions, which was formerly reported as 6 months, was 2 years in the present series[24].

The incidence of HU-related SCCs and BCCs was 0.09% in a multicenter cohort study of 3,411 patients receiving HU[29], but it reached 7.7% in a small series[30]. Furthermore, 30.8% of the patients also had AKs in the latter series[30]. Although some previous studies have reported SCCs as a developing skin cancer type more commonly in association with HU therapy[27,30,31], one large series (BCCs, n=3; SCCs, n=3)[29] and the present series (BCCs, n=12; SCCs, n=12) showed an equal prevalence of both NMSC types (Table 2). In a large study evaluating patients treated with HU, busulfan, or radioactive phosphorus, BCC was more commonly seen than SCC[16]. The concurrence of SCCs and BCCs was previously reported, and it was also seen in three of the patients in the present series[25,32]. In five of the eight patients with SCC in the present series, AKs were also associated.

The face, especially the nose and forehead, is the most common location of NMSCs in our series, followed by other sun-exposed locations such as the scalp, neck, and extensor surfaces of the arms. Although all SCCs occurred on sun-exposed areas such as the head, neck, and arm in the present series, none of them developed on the vermilion border of the lip. However, SCC was previously reported on the lower lip mucosa in association with HU[27]. SCC occurred in the ear in one patient of the present series and in another patient from the literature[27,33]. Furthermore, HU-associated SCCs were also reported to occur in some other body areas that are not exposed to the sun such as the heel[34] and intraoral mucosa[35]. In the present series, two BCCs occurred on the trunk. Three patients had more than one SCC, like some other cases that were reported previously[36-38]. Although HU-associated metastatic SCCs were occasionally reported in the literature[25,39], none of the SCCs had become metastatic in the present series during the follow-up period.

In the present series, the superficial BCC was the most common BCC type, followed by nodular (nodulo-ulcerative) and morpheaform types. Two patients had more than one BCC. BCC subtypes in patients using HU were not described previously.

Contrary to the high incidence of secondary NMSCs, melanoma, which is another malignant tumor usually related to UV, was occasionally reported in patients on HU therapy[31,40,41]. In a study evaluating secondary cancers, among 1,881 patients with myeloproliferative neoplasms, melanoma was seen in 4.9%, and the rate of melanoma was relatively higher in patients with polycythemia vera[13]. However, the number of these patients under HU therapy was not stated. Kissova et al.[31] reported three melanomas in a cohort of 66 patients receiving HU therapy. Verner et al.[40] reported that 5 of 149 patients on HU therapy were diagnosed with melanoma. In the present series, *in situ* melanoma on the trunk accompanied by SCC was seen in one of the patients with chronic myeloid leukemia.

In addition, sebaceous adenoma, which was seen in one of the patients in the present series, in association with HU treatment has not been previously reported. Although this sebaceous gland tumor can be seen in association with solid neoplasia in the spectrum of Muir-Torre syndrome[42,43], it was not associated with chronic myeloproliferative diseases. Therefore, it may be an incidental finding.

Table 2. Reported large series presenting HU-associated precancerous lesions and malignant skin tumors

	Total number of patients under HU therapy	Total number of patients with skin tumors	AK	SCC number of patients/number of lesions	BCC number of patients/number of lesions	Other cutaneous malignancies (number of patients)
Our series	N/A	13	9	8/12	6/12	*In situ* melanoma (1)
Antonioli et al.[29]	3411	10	7	3/3	3/3	-
Vassallo et al.[27]	158	5	-	3/3	-	Keratoacanthoma (2)
Salmon-Ehr et al.[30]	26	10	8	2/2	-	-
Gómez et al.[16]	312	43	-	30*	36*	-
Kissova et al.[31]	66	9	-	?/5	?/3	Melanoma (3)

*In this study, a total of 36 BCCs and 30 SCCs were seen in 51 patients, but only 43 of them had used HU and eight of them were exposed to busulfan and radioactive phosphorus. AK: Actinic keratoses, BCC: Basal cell carcinoma, N/A: Not available, SCC: Squamous cell carcinoma, HU: Hydroxyurea

Some studies have reported the occurrence of new skin tumors after HU therapy cessation[44,45]. In the present series, three patients had skin tumors after HU therapy cessation. Because of the development of chronic skin malignancies associated with HU therapy, a regular patient follow-up is necessary.

Study Limitations

This study has some limitations. This is a single-center study was conducted via the collaboration of only the dermatology and pathology departments without the contribution of the hematology department. The study mainly aimed to determine the real incidence of precancerous skin lesions and malignant skin tumors in a cohort of patients receiving HU therapy. HU was not the single cytoreductive drug used in most patients, which made the interpretation of its role in cutaneous malignancy development more difficult.

Conclusion

AK and NMSCs, particularly involving the sun-exposed areas of the body, are important problems of patients on long-term HU regardless of their primary hematological disorders. While the incidence of BCC and SCC are comparable, the superficial and nodular BCCs more commonly occur in association with HU therapy. Most patients have a history of long-term HU therapy, but even a short-term treatment may induce such lesions. The duration from the initiation of HU to the onset of these lesions may be up to 10 years. Given this lifelong risk, protective measures against sunlight and a long-term follow-up should be recommended for all patients treated with HU. Whether there is an association between melanoma and HU treatment as seen in one of our patients should be verified by further studies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee (approval number: 12, date: 11.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.B., K.N.B., S.K.S., Ş.Ö.S., A.M., N.B., Design: C.B., K.N.B., S.K.S., Ş.Ö.S., A.M., N.B., Data Collection or Processing: C.B., K.N.B., S.K.S., Ş.Ö.S., A.M., N.B., Analysis or Interpretation: C.B., K.N.B., S.K.S., Ş.Ö.S., A.M., N.B., Literature Search: C.B., K.N.B., S.K.S., Ş.Ö.S., A.M., N.B., Writing: C.B., K.N.B., S.K.S., Ş.Ö.S., A.M., N.B.

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References

1. Ferrari A, Carobbio A, Masciulli A, et al.: Clinical outcomes under hydroxyurea treatment in polycythemia vera: a systematic review and meta-analysis. Haematologica 2019;104:2391-9.
2. Algiraigri AH, Kassam A: Hydroxyurea for hemoglobin E/ -thalassemia: a systematic review and meta-analysis. Int J Hematol 2017;106:748-56.
3. Algiraigri AH, Wright NAM, Paolucci EO, Kassam A: Hydroxyurea for lifelong transfusion-dependent β-thalassemia: a meta-analysis. Pediatr Hematol Oncol 2017;34:435-48.
4. Vick L, Potts M, Jaskowiak M, Gibson RW: Hydroxyurea adherence strategies for persons with sickle cell disease: A systematic review. J Health Care Poor Underserved 2021;32:99-118.
5. Renneville A, Patnaik MM, Chan O, Padron E, Solary E: Increasing recognition and emerging therapies argue for dedicated clinical trials in chronic myelomonocytic leukemia. Leukemia 2021;35:2739-51.
6. Ruzzon E, Randi ML, Tezza F, Luzzatto G, Scandellari R, Fabris F: Leg ulcers in elderly on hydroxyurea: a single center experience in Ph- myeloproliferative disorders and review of literature. Aging Clin Exp Res 2006;18:187-90.
7. Wiechert A, Reinhard G, Tüting T, Uerlich M, Bieber T, Wenzel J: Multiple kutane neoplasien nach therapie mit hydroxyurea [multiple skin cancers in a patient treated with hydroxyurea]. Hautarzt 2009;60:651-4.
8. Sanchez-Palacios C, Guitart J: Hydroxyurea-associated squamous dysplasia. J Am Acad Dermatol 2004;51:293-300.
9. Cantisani C, Kiss N, Naqeshbandi AF, et al.: Nonmelanoma skin cancer associated with hydroxyurea treatment: overview of the literature and our own experience. Dermatol Ther 2019;32:e13043.
10. Bulte CA, Hoegler KM, Kutlu Ö, Khachemoune A: Hydroxyurea: a reappraisal of its cutaneous side effects and their management. Int J Dermatol 2021;60:810-7.
11. Lacouture M, Sibaud V: Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. Am J Clin Dermatol 2018;19:31-9.
12. Wu JH, Cohen DN, Rady PL, Tyring SK: BRAF inhibitor-associated cutaneous squamous cell carcinoma: new mechanistic insight, emerging evidence for viral involvement and perspectives on clinical management. Br J Dermatol 2017;177:914-23.
13. Barbui T, Ghirardi A, Masciulli A, et al.: Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia 2019;33:1996-2005.
14. Brabrand M, Frederiksen H: Risks of solid and lymphoid malignancies in patients with myeloproliferative neoplasms: clinical implications. Cancers (Basel) 2020;12:3061.
15. Gavini DR, Salvi DJ, Shah PH,Uma D, Lee JH, Hamid P: Non-melanoma skin cancers in patients on hydroxyurea for Philadelphia chromosome-negative myeloproliferative neoplasms: A systematic review. Cureus 2021;13:e16978.
16. Gómez M, Guillem V, Pereira A, et al.: Risk factors for non-melanoma skin cancer in patients with essential thrombocythemia and polycythemia vera. Eur J Haematol 2016;96:285-90.
17. Harrison CN, Vannucchi AM, Kiladjian JJ, et al.: Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia 2016;30:1701-7.
18. Verstovsek S, Vannucchi AM, Griesshammer M, et al.: Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. Haematologica 2016;101:821-9.
19. Polverelli N, Elli EM, Abruzzese E, et al.: Second primary malignancy in myelofibrosis patients treated with ruxolitinib. Br J Haematol 2021;193:356-68.
20. Mora B, Rumi E, Guglielmelli P, et al.: Second primary malignancies in postpolycythemia vera and postessential thrombocythemia myelofibrosis: a study on 2233 patients. Cancer Med 2019;8:4089-92.
21. Blechman AB, Cabell CE, Weinberger CH, et al.: Aggressive skin cancers occurring in patients treated with the Janus kinase inhibitor ruxolitinib. J Drugs Dermatol 2017;16:508-11.
22. Aboul-Fettouh N, Nijhawan RI: Aggressive squamous cell carcinoma in a patient on the Janus kinase inhibitor ruxolitinib. JAAD Case Rep 2018;4:455-7.
23. Yarbro JW: Mechanism of action of hydroxyurea. Semin Oncol 1992;19(Suppl 9):1-10.
24. Saraceno R, Teoli M, Chimenti S: Hydroxyurea associated with concomitant occurrence of diffuse longitudinal melanonychia and multiple squamous cell carcinomas in an elderly subject. Clin Ther 2008;30:1324-9.
25. Disdier P, Harle JR, Grob JJ, Weiller-Merli C, Magalon G, Weiller PJ: Rapid development of multiple squamous-cell carcinomas during chronic granulocytic leukemia. Dermatologica 1991;183:47-8.
26. SchleussingerTM, Dyall-Smith D, Field LM: Hydroxyurea-associated squamous dysplasia in a monozygotic twin. J Am Acad Dermatol 2011;65:679-80.
27. Vassallo C, Passamonti F, Merante S, et al.: Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. Clin Exp Dermatol 2001;26:141-8.

28. Malato A, Rossi E, Palumbo GA, Guglielmelli P, Pugliese N: Drug-related cutaneous adverse events in Philadelphia chromosome-negative myeloproliferative neoplasms: a literature review. Int J Mol Sci 2020;21:3900.
29. Antonioli E, Guglielmelli P, Pieri L, et al.: Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. Am J Hematol 2012;87:552-4.
30. Salmon-Ehr V, Leborgne G, Vilque JP, Potron G, Bernard P: Secondary cutaneous effects of hydroxyurea: prospective study of 26 patients from a dermatologic consultation. Rev Med Interne 2000;21:30-4.
31. Kissova J, Ovesna P, Penka M, Bulikova A, Kiss I: Second malignancies in Philadelphia-negative myeloproliferative neoplasms-single-center experience. Anticancer Res 2014;34:2489-96.
32. Radić J, Batinac T, Hadžisejdić I, Načinović-Duletić A, Valković T, Jonjić N: Concurrent basal cell and squamous cell carcinomas associated with hydroxyurea therapy. Acta Dermatovenerol Croat 2011;19:183-6.
33. García-Martínez FJ, García-Gavín J, Alvarez-Pérez A, Alonso-González J, Ginarte M, Toribio J: Scleroderma-like syndrome due to hydroxyurea. Clin Exp Dermatol 2012;37:755-8.
34. Stone T, Berger A, Blumberg S, et al.: A multidisciplinary team approach to hydroxyurea-associated chronic wound with squamous cell carcinoma. Int Wound J 2012;9:324-9.
35. De Benedittis M, Petruzzi M, Giardina C, Lo Muzio L, Favia G, Serpico R: Oral squamous cell carcinoma during long-term treatment with hydroxyurea. Clin Exp Dermatol 2004;29:605-7.
36. Aste N, Fumo G, Biggio P: Multiple squamous epitheliomas during long-term treatment with hydroxyurea. J Eur Acad Dermatol Venereol 2001;15:89-90.
37. Neill B, Ryser T, Neill J, Aires D, Rajpara A: A patient case highlighting the myriad of cutaneous adverse effects of prolonged use of hydroxyurea. Dermatol Online J 2017;23:13030/qt8h64503t.
38. De Simone C, Guerriero C, Guidi B, Rotoli M, Venier A, Tartaglione R: Multiple squamous cell carcinomas of the skin during long-term treatment with hydroxyurea. Eur J Dermatol 1998;8:114-5.
39. Pamuk GE, Turgut B, Vural O, Demir M, Tek M, Altaner S: Metastatic squamous cell carcinoma of the skin in chronic myeloid leukaemia: complication of hydroxyurea therapy. Clin Lab Haematol 2003;5:329-31.
40. Verner E, Forsyth C, Grigg A: Cyclical thrombocytosis, acquired von Willebrand syndrome and aggressive non-melanoma skin cancers are common in patients with Philadelphia-negative myeloproliferative neoplasms treated with hydroxyurea. Leuk Lymphoma 2014;55:1139-43.
41. Saito A, Fujisawa Y, Maruyama H, et al.: Subungual melanoma complicated by hydroxyurea-induced melanonychia with non-melanoma Hutchinson's sign. Eur J Dermatol 2018;28:559-61.
42. John AM, Schwartz RA: Muir-Torre syndrome (MTS): an update and approach to diagnosis and management. J Am Acad Dermatol 2016;74:558-66.
43. Ponti G, Ponz de Leon M: Muir-Torre syndrome. Lancet Oncol 2005;6:980-7.
44. Estève E, Georgescu V, Heitzmann P, Martin L: Multiple skin and mouth squamous cell carcinomas related to long-term treatment with hydroxyurea. Ann Dermatol Venereol 2001;128:919-21.
45. Best PJ, Petitt RM: Multiple skin cancers associated with hydroxyurea therapy. Mayo Clin Proc 1998;73:961-3.