Tasa de curación clínica con 5-fluorouracilo al 5% tópico para el manejo del carcinoma basocelular superficial de bajo riesgo

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RESUMEN

Introducción/objeto: El carcinoma basocelular superficial (CBCs) representa un subtipo clínico e histopatológico del cáncer más frecuente en el mundo. La resección quirúrgica es el tratamiento de primera línea; sin embargo, existen modalidades terapéuticas no quirúrgicas más costoefectivas y con mejores desenlaces cosméticos, como el 5-fluorouracilo (5-FU) al 5%. El objetivo de este estudio fue evaluar la tasa de curación clínica, la tolerabilidad y los niveles de satisfacción en pacientes con piel de pigmentación intermedia en el tratamiento del CBCs de bajo riesgo con 5-FU tópico al 5%.

Métodos: Se realizó un estudio prospectivo tipo serie de casos entre junio de 2014 y agosto de 2018 en el Servicio de Dermatología del Hospital de San José en Bogotá, Colombia. Se incluyeron pacientes con diagnóstico de CBCs confirmado por histopatología. Se les administró 5-FU al 5% en ungüento, dos veces al día, durante ocho semanas. Las evaluaciones clínicas presenciales fueron hechas en la semana 4 y en la semana 8. Una vez se estableció la curación clínica, se inició el seguimiento trimestral.

Resultados: Un total de 19 pacientes con 23 lesiones participaron en el estudio. El período de seguimiento osciló entre 7 y 48 meses y la mediana de seguimiento fue de 38 meses. Se logró la curación clínica global en el 95,45% de las lesiones tratadas (21/22). Además, se observó que la cicatriz residual posttreatment fue disminuyendo progresivamente de tamaño.

Conclusión: El tratamiento del CBCs en zonas de mediano y bajo riesgo con 5-FU al 5% tópico durante ocho semanas mostró una tasa de curación clínica del 95%, con un porcentaje alto de satisfacción y un sobresaliente grado de tolerabilidad.

PALABRAS CLAVE: 5-fluorouracilo; Cáncer de piel no melanoma; Carcinoma basocelular superficial; Quimioterapia tópica; Tratamiento.
CURE RATE OF LOW-RISK SUPERFICIAL BASAL CELL CARCINOMA TREATED WITH TOPICAL 5-FLUOROURACIL

SUMMARY

Background/objective: Basal cell carcinoma (BCC) is the most common cancer in the world, making this condition a public health issue. Superficial BCC (sBCC) is a subtype with indolent behavior. The gold standard treatment is surgical resection; however, sBCC can be treated with more cost-effective non-invasive therapies such as 5% 5-fluorouracil (5-FU). The aim of this study was to evaluate the clinical cure rate, tolerability, and satisfaction levels in patients with intermediate pigmented skin in the treatment of low-risk sBCC with topical 5% 5-FU. Methods: A prospective case series study was conducted between June 2014 and August 2018 at the department of dermatology of Hospital de San José in Bogotá, Colombia with histologically-proven sBCC lesions. Lesions were treated with topical 5% 5-FU twice daily for up to 8 weeks. A follow-up evaluation was conducted at weeks four and eight during treatment. Follow-up was planned to be conducted every three months. Results: The study included 19 patients with 23 biopsy-proven sBCC lesions. Twenty-two lesions completed treatment with 5% 5-FU cream. The follow-up period ranged between 7 and 48 months, and the median follow-up time was 38 months (IQR: 21-48). All study patients had intermediate or higher pigmented skin. Clinical cure was achieved in 95.45% of treated lesions. Conclusion: The efficacy rate of 5% 5-FU for an 8-week treatment for sBCC located in intermediate and low-risk areas was 95%, offering high levels of patient satisfaction with an outstanding tolerability profile. Key Words: 5-fluorouracil; Non melanoma skin cancer; Superficial basal cell carcinoma; Topical chemotherapy; Treatment.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in the world, with a high incidence estimated at 2 million new cases annually, making this condition a public health issue and a large burden on healthcare services (1). Superficial basal cell carcinoma (sBCC) is a histological subtype with indolent behavior (2). The gold standard of treatment for the majority of sBCC is surgical resection; however, sBCC can also be treated with non-invasive and more cost-effective non-surgical treatment modalities, which may achieve complete tumor eradication, particularly in those with indolent growth (3,4).

The absolute incidence of BCC is difficult to establish, but its overall incidence is clearly on the rise (5). An estimate of BCC incidence rates in the United States is 407 cases per 100,000 Caucasian men and 212 cases per 100,000 Caucasian women. Although incidence rates are higher among elderly male populations, a particularly large increase has been noticed among young female populations (6,4). Worldwide, the annual incidence varies widely. A recent meta-analysis evaluating the global incidence of non-melanoma skin cancer found the highest rates in Australia (>1000/100,000 persons/year) and the lowest rates in Africa (<1/100,000 persons/year). Incidence rates in England were 121.29/100,000 persons per year, and in Spain, the overall incidence was estimated at 113.05/100,000 persons per year (7,8).

The worldwide high incidence rates underscore the importance of non-surgical alternatives. They are safe, easy to access, and cheaper. Topical treatments with good cure rates include imiquimod, 5% 5-fluorouracil (5-FU), and photodynamic therapy (PDT) (3,9-11). They may also offer good oncologic results, reduce the risk of poor healing and infection, and achieve good cosmetic outcomes.
Imiquimod is the most frequently used topical therapy with total cure rates between 75% and 85% (12, 13). On the other hand, 5% 5-FU was the first FDA-approved topical treatment for sBCC, with reported success rates of up to 93%; however, few studies on the efficacy of this therapy have been carried out, and there is no information on patients with intermediate skin phototypes (14-16). The objective of this study was to evaluate the clinical cure rate, tolerability, and satisfaction levels in patients with intermediate pigmented skin in the treatment of low-risk superficial basal cell carcinoma with topical 5% 5-FU.

MATERIALS AND METHODS

A prospective case series study was conducted between June 2014 and August 2018 at the outpatient dermatology service of Hospital de San José in Bogotá, Colombia. Patients older than 18 years of age who met the inclusion criteria were included. Inclusion criteria included histologically-proven superficial BCC lesions, reviewed by a dermatopathologist, located on an intermediate-risk area of the face measuring less than or equal to 10 mm, or lesions on the trunk or extremities measuring less than or equal to 20 mm. For women of reproductive age, only those willing to use a contraceptive method during therapy were recruited.

Patients with recurrent sBCC, a diagnosis of BCC with a mixed histopathological pattern, or who had received any topical treatment indicated for sBCC in the last 30 days were excluded from the study. Also excluded were patients with hypersensitivity to topical 5-FU, peri-ocular sBCC, immunosuppressive conditions, or a diagnosis of inflammatory skin diseases compromising the treatment area with 5-FU (such as atopic dermatitis, psoriasis, or contact dermatitis).

Lesions were treated with 5% 5-FU cream twice daily for up to 8 weeks with a 1-mm thick 1-cm surrounding margin. Follow-up evaluations were conducted at weeks four and eight during treatment.

Adverse events (AEs) were evaluated at the end of weeks 4 and 8 of treatment. Treatment could be paused for up to 8 days if patients reported local skin reactions such as extreme irritation, severe pain, burning, and inflammation. The response to treatment was clinically assessed at week 12. Clinical cure was defined as achieving complete disappearance of lesions, erythema, and scaling.

Patients with clinically resolved lesions underwent follow-up every three months for 18 months, followed by periodic 6-month follow-ups for a maximum of 5 years. Skin biopsies were performed on clinically suspicious lesions. Cases with histological evidence of tumor recurrence were considered therapeutic failures and underwent surgical excision.

Instruments to measure and evaluate variables established by the study protocol, such as tumor size, patient satisfaction, and side effects, were designed. Patient photographs were taken and stored on a hard disk drive (HDD) during each follow-up visit for monitoring progress. Data analysis was performed using Stata13® software and Microsoft Excel 2010.

This study was approved by the Hospital de San José Ethics Committee for Research Involving Human Beings.

RESULTS

The study included 19 patients with 23 biopsy-proven sBCC lesions. One patient withdrew from the study in week 4 due to severe application-site irritation. Twenty-two lesions completed treatment with 5% 5-FU cream twice daily for up to 8 weeks. No patients were lost to follow-up.

The study population predominantly comprised males (11 men vs 8 women), with an average age of 74 years (IQR 66-99). The majority of patients were skin phototype III (12/19, 63.2%), followed by phototype IV (4/19, 21.1%) and phototype II (3/19, 15.8%). Twelve patients lived in an urban area and 7 in rural areas. Most of the sBCC lesions were located on the trunk (13/22, 59%) and the head (8/22, 36.6%); only one treated patient had lesions on the upper limbs (1/22, 4.5%) (Figure 1).
The follow-up period varied between 7 and 49 months, with a median follow-up time of 38 months (IQR 21-48) (Figure 2). Eighteen out of 22 lesions completed the minimum 18 months of follow-up as established by the study protocol. All patients continued with oncological controls every six months, and more than 9 lesions completed a follow-up of more than 40 months, with 3 lesions reaching 49 months of follow-up.

The most common adverse events were mild to moderate edema and erythema, and only one case presented with extremely severe irritation, showing severe erythema, weeping, erosion, and ulceration of the skin. Regarding treatment tolerability, more than 80% of patients reported that edema and pain were mild at the end of weeks 4 and 8 (Figure 3).

Figure 1. Schematic location of the 23 lesions.

Figure 2. The box plot of follow-up time in months shows a median follow-up time of 38 months. Fifty percent of patients achieved a follow-up duration between 21 and 49 months.
drawn from the study and underwent surgical excision of their lesion. No infections or treatment-related complications occurred, such as hypertrophic scars or functional or cosmetic defects.

Clinical cure was achieved in 95.45% of treated lesions (21/22). Patients also showed progressive reduction in the size of post-treatment scars and disappearance of residual erythema (Figure 4). Cosmetic appearance improved during follow-up (Figure 5).

As established by the study protocol, clinical cure was assessed in week 12. Nineteen lesions met the full criteria for clinical cure (complete disappearance of lesions, tumor erythema, and scaling). Fifteen lesions presented erythema; however, this finding was attributed to the residual local effects of 5-FU and therefore was not considered as tumor erythema. All lesions (100%) were cured by week 12. Nevertheless, three patients underwent a control biopsy, finding histological evidence of tumor recurrence in only one patient documented during the second follow-up. This patient was withdrawn from the study and underwent surgical excision of their lesion. No infections or treatment-related complications occurred, such as hypertrophic scars or functional or cosmetic defects.

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Figure 3. Level of edema, erythema and pain at weeks 4 and 8.
*n=23, on week 4; n=22 at week 8 (one patient dropped out from treatment regime).

Figure 4. Median size of scar during follow-up.
DISCUSSION

Five percent 5-fluorouracil (5-FU) was the first topical treatment for superficial BCC approved by the US Food and Drug Administration (FDA) \(^{(15)}\). Approval was based on a study of 113 sBCC lesions in 54 patients which demonstrated a 93% “success rate”. This data were confirmed in the 5-FU efficacy and tolerability study conducted by Gross et al. in 29 patients and 31 lesions, treated for 12 weeks, achieving complete histological clearance in 90% of lesions \((28/31)\). However, these studies did not report data on long-term follow-up \(^{(15)}\).

Photodynamic therapy was compared to topical imiquimod and topical 5% 5-FU in a study conducted in Holland by Arits et al. in 2012. The results showed that imiquimod was superior and 5-FU not inferior to photodynamic therapy. The overall success rate was 72.1% for imiquimod, 80.1% for 5-FU, and 83.4% for PDT \(^{(16)}\).

The patient treatment satisfaction measure at the end of Week 12 was as follows: 47.4% were satisfied, and 52.6% were completely satisfied, with no patients expressing dissatisfaction (Figure 6).

**Figure 5.** Example of the cosmetic appearance of three random lesions. Comparison between day 1 and follow-up.

**Figure 6.** Satisfaction rate at week 12.
In 2017, Jansen et al. published the first prospective study with a head-to-head comparison of three different non-invasive treatments for sBCC and a five-year follow-up period (9). The latter constitutes the continuation of a three-year analysis made by Roozeboom et al. in 2015 on the same study population that demonstrated the probability of total tumor-free survival at 5 years of 80.5% for imiquimod treatment, 70% for 5-FU, and 62.7% for photodynamic therapy. These results confirm that 5-FU is not inferior to photodynamic therapy and other therapies (9-17).

Among the strengths of this study is the inclusion of only Latinos/Hispanics, mostly characterized by high III and IV skin phototypes (n: 16, 84%), in which treatment tolerability has not been previously studied. Although follow-up after the end of treatment was mainly clinical, a histologic evaluation was made in cases with clinically suspicious lesions of tumor recurrence (n: 3, 16.6%). The study was limited by the small sample size and because it was a single-center trial.

CONCLUSION

The efficacy rate of 5% 5-FU for 8 weeks of treatment for sBCC located in intermediate and low-risk areas was 95%, offering high levels of patient satisfaction with an outstanding tolerability profile.

ACKNOWLEDGEMENTS

To all Dermatology residents of the Fundación Universitaria de Ciencias de la Salud (FUCS) for their commitment in the follow-up process. Also, to Claudia Ibañez (FUCS Research Division) for her collaboration in the preparation of the manuscript.

Key points

- Superficial basal cell carcinoma (sBCC) is a subtype of basal cell carcinoma with slow-growing and indolent behavior.
- The gold standard of treatment is surgical resection; nevertheless, sBCC can also be treated with non-surgical treatment modalities which may be more cost-effective and offer outstanding cosmetic outcomes.
- Few studies on the efficacy of topical 5% 5-FU have been conducted, and there is no information on patients with intermediate skin phototypes.
- Topical 5% 5-FU is a low-cost therapy for sBCC, easy to access, and with good tolerability and satisfaction levels.
Puntos clave

- El carcinoma basocelular (CBC) superficial es una forma de presentación clínica del CBC considerada de baja agresividad y crecimiento lento.

- La resección quirúrgica es el tratamiento de primera línea, aunque existen tratamientos no quirúrgicos más costeefectivos y con mejores desenlaces cosméticos.

- Hay pocos estudios que hayan evaluado la eficacia del 5-FU al 5% en el tratamiento del carcinoma basocelular superficial y ninguno en pacientes latinos.

- El 5-FU al 5% es una terapia tópica de fácil administración, de bajo costo y con un buen perfil de tolerancia y satisfacción terapéutica.

REFERENCES


