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REVIEW

Nonsurgical Therapies for Basal Cell Carcinoma: A Review☆

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Abstract Basal cell carcinoma (BCC) is the most prevalent malignant tumor in humans and the local destruction of tissue that can result from excision has a significant impact on well-being. Treating BCC is costly for health care systems given the high incidence of this tumor, especially in older patients. Standard treatment involves either resection with histologic assessment of margins or Mohs micrographic surgery. Surgery is sometimes contraindicated, however, due to the presence of significant comorbidity or high cosmetic expectations. For such patients, nonsurgical treatments have become available. These alternatives can offer good local control of disease, preserve function, and achieve excellent cosmetic results.

PALABRAS CLAVE
Carcinoma basocelular;
Cáncer de piel;
Tratamiento

Terapias no quirúrgicas para el carcinoma basocelular: revisión

Resumen El carcinoma basocelular (CBC) es el tumor maligno más frecuente en seres humanos, y tiene la capacidad de causar una significativa morbilidad asociada a su potencial de destrucción local. El tratamiento del CBC demanda altos costes de atención para los sistemas de salud, por la gran incidencia de esta enfermedad, especialmente en pacientes mayores. El tratamiento estándar para la mayoría de los CBC consiste en la resección quirúrgica con márgenes y control histológico de los bordes de sección, o mediante cirugía micrográfica de Mohs. Sin embargo, en algunos pacientes con contraindicación para cirugía, que tienen comorbilidades importantes o altas expectativas estéticas, existen en la actualidad nuevas alternativas terapéuticas no quirúrgicas, con las cuales se puede lograr muy buen control local, preservar la función y obtener un excelente resultado cosmético.

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Introduction

Basal cell carcinoma (BCC) is the most common cancer in humans.[1,2] Although it rarely metastasizes, it can cause significant morbidity due to the invasion and destruction of neighboring anatomic structures.[3]

Australia has the highest incidence of nonmelanoma skin cancer (NMSC) in the world, with an age-standardized rate of 213 cases per 100 000 males and 113 cases per 100 000 females.[4,5] In Spain, the crude incidence of BCC is 113.05 cases per 100 000 inhabitants per year (95% CI, 89.03-137.08),[6–8] and according to estimates from the United States, over 2 million cases of NMSC were diagnosed in 2013.[9,10]

The annual cost of treating NMSC in the US population has been estimated at over $420 million,[11,12] and according to data published in 2009, over £240 million was spent on NMSC treatment in England in 2002.[13,14]

Surgery is the established treatment of choice for BCC for 2 main reasons: it offers the highest cure rates and permits histologic control of margins.[7] The emergence of nonsurgical alternatives, however, means that excellent oncologic and cosmetic results are now possible in subgroups of patients with BCC with a low risk of recurrence or in whom surgery is contraindicated for medical reasons. The aim of this article was to review the literature on the nonsurgical treatment of BCC.

Method

We performed a literature review to identify articles and clinical practice guidelines discussing the nonsurgical management of BCC that were published in the following databases between 2006 and 2016: MEDLINE via Ovid, EMBASE, Lilacs, and the Cochrane Library. We also performed a hand search.

Studies in which patients had received nonsurgical treatment for BCC were included. We excluded studies in nonhumans, economic evaluations, case series, personal opinion articles, and letters to the editor (Fig. 1).

The initial search retrieved 639 articles, 466 of which were excluded (Fig. 1). The articles that met the inclusion criteria were reviewed separately by 2 authors and any discrepancies were resolved by a third author.

Thirty-seven articles were analyzed for the section on the medical treatment of BCC; 20 of these were reviewed in 4 systematic reviews, 2 of which included a meta-analysis. There were also 7 clinical trials, 6 review articles, and 2 clinical management guidelines evaluating different treatments for BCC. The 17 remaining articles used for this section were evaluated in the systematic reviews included. The methodological quality of the systematic reviews assessed using AMSTAR was high in 3 cases and acceptable in 1 (Table 1). The characteristics of the clinical trials are summarized in Table 2.

Factors That Determine Choice of Medical Treatment

To choose the most appropriate medical treatment for BCC, it is important to be familiar with the different predictors of local recurrence in order to categorize the risk for individual lesions (Table 3).

Histologically, BCC can be classified into 2 subtypes: an indolent-growth subtype (nodular and superficial BCCs) and an aggressive-growth subtype (morpheaform, infiltrative, micronodular, and basosquamous BCCs). Distinct histopathologic patterns can coexist in a single tumor, in which case the pattern is referred to as a *mixed pattern*.[3,15–17]

Locally advanced BCC is an important category. These tumors are characterized by long duration, a history of multiple recurrences, and considerable facial disfigurement resulting from tumor growth and previous surgery. The chance of surgical cure in such cases is low or nonexistent.

Medical Treatments for BCC

Numerous medical treatment modalities have been described for BCC, including topical imiquimod, 5-fluorouracil (5-FU), photodynamic therapy (PDT), intralesional interferon (IFN), radiation therapy, and Hedgehog (Hh) pathway inhibitors (Table 4).

Imiquimod

Imiquimod 5% is a toll-like receptor agonist approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of primary superficial BCCs with a diameter of less than 2 cm. It is believed to induce IFN-α, tumor necrosis factor-α, and other cytokines that activate T helper 1 cells, which, in turn, induce an antitumor immune response.[18]

The first study to evaluate imiquimod in the treatment of superficial BCC was published in 1999.[19] It was a clinical trial that compared 3 treatment regimens: imiquimod twice a day, imiquimod once a day, and imiquimod 3 times a week. Histologically confirmed complete response was observed in the 3 groups on completion of treatment. The complete response rate was 60% in the group of patients who received 2 doses a week, and 50% in the group that received treatment once a week.

A systematic review of treatment success in primary superficial BCC published in 2012 by Roozeboom et al.[20] reported an estimated complete response rate of 86.2% (95% CI, 82%-90%) for imiquimod after a follow-up period of 6 to 19 weeks. The 1-year tumor-free survival rate based on pooled estimates from 23 studies was 87.3% (95% CI, 84%-91%). The authors concluded that imiquimod was an effective treatment for superficial BCC with a maximum diameter of 2 cm.

The British Association of Dermatologists guidelines for the management of BCC rate the use of topical imiquimod with a quality of evidence I and a strength of recommendation A.[21] The use of histologic verification[22–26] and follow-up periods of up to 5 years[27–29] in the studies reviewed to draw up these guidelines adds strength to the effectiveness of imiquimod in the treatment of superficial BCC. The final study reports drawn up by Gollnick et al.[27,28] showed 5-year histologic clearance rates of 85.4% and 86.9% for patients with superficial BCC treated with imiquimod 5 times and 7 times a week for a period of 6 weeks, respectively.