BASAL CELL CARCINOMA: WHEN EXCISION IS NOT AN OPTION

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Abstract

Basal cell carcinomas are the most common malignant skin tumors. The clinical aspect underlying this type of tumor ranges from millimeter lesions to large, ulcerated tumors. Although surgery remains the gold standard of treatment for most of the high-risk tumors, recent nonsurgical and topical therapies, used in mono- or combination therapy have offered a new perspective in the treatment of basal cell carcinoma. Causes related to patient's associated pathology, location and tumor characteristics, recovery times, costs, and patient's desire have led to the exploration of other treatment options.
In this paper we propose to revise the current indications for treatment of basal cell carcinomas, the international experience of combined therapies as it appears from articles published in specialized journals.

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Introduction

Non-melanoma skin cancer (NMSC) is the most frequent cancer found in fair-skinned individuals. The etiology of NMSC involves genetic, environmental and phenotypic factors (1). Basal cell carcinoma (BCC) is a slow-growing, locally invasive malignant skin tumor; metastasis is rare, but the tumor can cause local tissue invasion and distruction (2).

The most common types of BCC are nodular, superficial and sclerodermiform. Other types are represented by: pigmented BCC, ulcerative and distructive forms. Four histological subtypes are described: superficial, nodular, infiltrative and morpheaform (3).

Although surgery remains the gold standard of treatment for most of the high-risk tumors, recent nonsurgical and topical therapies, used in mono- or combination therapy have offered a new perspective in the treatment of BCC (4). They aim to increase patient comfort and cosmetic outcome, to reduce treatment duration and costs and to offer complete clearance and no recurrence (5).

Patient and treatment selection

Careful evaluation of the patient and the specific factors related to the tumor are important for establishing the proper treatment (4).

Tumor related factors relevant to the treatment are: type, size (area greater than 1 to 2 cm) and if the tumor is reccurent or not. Equaly important are the duration of evolution, growth rate, indistinct margins, aggressive histologic pattern, and certain anatomic locations. High-risk sites may include eyelids, nose, ears, medial chantus, nasolabial fold, scalp, lip, fingers, toes and genitals. Patient related factors include age, medical status, concomitent medication (6). For example, for patients receiving antiagregant or anticoagulant medication, one may choose a nonsurgical treatment. Also, factors such as the patient's preference, costs, local availibility of certain therapies, training of the treating physician may dictate the treatment options (4).

Treatment methods

Destructive surgical and nonsurgical techniques are indicated for low-risk tumors (4). Curettage and

Type of treatment	Evidence levels
Destructive techniques: surgical nonexcisional	
1. Curettage and cautery	Curettage and cautery is a good treatment for low risk BCC. (*Strength of recommendation A, quality of evidence II-iii*)
2. Cryosurgery	Cryosurgery is a good treatment for low-risk BCC. (*Strength of recommendation A, quality of evidence II-ii*)
3. Carbon dioxide laser	Carbon dioxide laser ablation may be effective in the treatment of low-risk BCC. (*Strength of recommendation C, quality of evidence III*)
Destructive techniques: nonsurgical	
Medical	
1. Topical immunotherapy with imiquimod	Topical imiquimod appears effective in the treatment of primary small superficial BCC. (*Strength of recommendation A, quality of evidence I*) Topical imiquimod may possibly have a role in the treatment of primary nodular BCC. (*Strength of recommendation C, quality of evidence I*)
2. Topical 5-fluorouracil	5-Fluorouracil appears effective for the treatment of superficial BCC (*Strength of recommendation A, quality of evidence I*)
Light based	
1. Photodynamic therapy	Photodynamic therapy is a good treatment for primary superficial BCC. (*Strength of recommendation A, quality of evidence I*)
2. Vascular selective lasers: Pulsed dye laser, Nd-yag	Photodynamic therapy is a reasonable treatment for primary low-risk nodular BCC. (*Strength of recommendation B, quality of evidence I*)

Table 1. Adapted from: Trakatelli M, Morton C, Nagore E, Ulrich C, Del Marmol V, Peris K, Basset-Seguin N. Update of the European guidelines for basal cell carcinoma management. *European Journal of Dermatology* 2014;24(3):312-329.

cautery, cryosurgery, laser ablation are destructive surgical methods; topical imiquimod, topical 5-fluorouracil (5-FU) and photodynamic therapy represent nonsurgical posibilities (Table 1).

Destructive treatment techniques: surgical

1. Curettage/electrodesiccation

These methods are appropiate for small, initial or superficial BCCs, but have the disadvantage that microscopic assessment of complete tumor removal is impossible. They are recommended for low-risk tumors located elsewhere than terminal hair areas (scalp, beard, pubic and axillary areas) beacause of the risk of tumor spreading to the follicular structures that might not be properly removed (7).

Curettage and cautery (electrodesiccation) can be used in combined therapy. Tumor debulking by curettage may be associated with imiquimod, photodynamic therapy and cryotherapy (4).

2. Cryosurgery

Cryosurgery is used to treat tumors by freeze-thaw cycles; it is a fast and cost-effective measure and can represent a means palliation for advanced tumors. A limitation is the poorer cosmetic outcome compared with other treatment options (7).

A recent study investigated cryosurgery for mid-face BCC; this involvement is considered as having a high risk of recurrence. The results indicated a 94% five years recurrence-free rate (8).

3. Ablative lasers

Ablative lasers may be used to remove cutaneous tumors, offering the advantage of thermal coagulation of the surgical margins. Laser ablation can be an effective treatment for the minimally invasive removal of superficial and early nodular BCCs (9). The lack of histoplatological control can be overcome by imaging techique guidance. The reflectance confocal microscopy (RCM) offers a noninvasive, cellular-level resolution imaging of the skin, which may guide and help improve the efficacy of the ablation procedure (10, 11).

Destructive treatment techniques: nonsurgical

Medical

1. Imiquimod

Imiquimod is a synthetic compound which belongs to a class of drugs referred to as imidazoquinolones. It acts as an immune response modifier in the body and has shown to have potent anti-viral and anti-tumoral activity. Imiquimod acts

both directly and indirectly on the innate and the adaptive immune responses. It binds to toll-like receptors (TLR) seven and eight of macrophages, monocytes, and dendritic cells and it induces apoptosis; this represents the direct action. Indirect action occurs by imiquimod inducing the release of immune modulatory cytokines (12). Treatment with imiquimod is generally well-tolerated, even in sensitive areas. Adverse effects are usually limited to application-site reactions and include erythema, edema, weeping, and pruritus. Cosmetic outcomes are generally excellent with imiquimod therapy, but hypopigmentation and scarring have been reported in a small percentage of cases (13).

Multiple randomized studies demonstrated the efficiency of imiquimod in treating multiple superficial BCC (4). A study published in 2015 in *British Journal of Dermatology* show a higher probability of treatment succes for imiquimod vs MAL-PDT for sBCC, with the exception of sBCC localized on the lower extremities in older patients (14).

2. 5-Fluorouracil

5-Fluorouracil is a pyrimidine analogue that preferentially affects DNA synthesis in neoplastic cells *via* inhibition of thymidylate synthase. Like other topical agents, this treatment is typically reserved for superficial BCCs. Some experts do not recommend the use of 5-FU for more aggressive BCCs due to prior studies that showed that 5-FU had a tendency to produce the appearance of superficial clearance, while tumor continues to grow in the deeper tissue (13). Adverse effects from the treatment with 5-FU, such as local skin reactions including erythema, blistering, erosions, and pruritus, are commonly described. Cosmetic results have been consistently reported as excellent, with high patient satisfaction (15).

Light based

1. Photodynamic therapy (PDT)

PDT is a noninvasive method, which is able to provide field treatment with good cosmetic results; it provides benefits to patients with superficial tumors. PDT can be associated with immunomodulatory agents (Imiquimod) and chemotherapeutic agents (5-FU, methotrexate, ingenol mebutate) (16).

High efficacy is demonstrated for PDT using standardized protocols in non-hyperkeratotic actinic keratoses, Bowen's disease, superficial basal cell carcinomas and in certain thin nodular BCC, with superiority of cosmetic outcome over conventional therapies. Recurrence rates following PDT are typically equivalent to existing therapies and higher than surgery for nodular BCC (17).

PDT uses five aminolevulinic acid (ALA) and its methylated form (MAL). After they are applied to the skin they will be metabolized to Protoporphyrin IX, a photosensitive compound that will be selective accumulated in the tumor cells (16, 18, 19).

Discomfort or pain is common during PDT. New studies identify patients most likely to experience discomfort and permit earlier adoption of pain-minimization strategies (17). Reviews of clinical trials reported cure rates ranging from 70% to 90% by using PDT for patients with BCC (7).

2. Vascular selective lasers

Basal cell carcinomas have supporting vasculature that serves as a target for vascular selective lasers. Pulsed dye laser and Nd:YAG laser are effective means of reducing tumor burden in patients with BCC (20).

Combined therapies

Combining laser surgery with adjunctive therapy, including intralesional or topical chemotherapy or immunotherapy, provides additional protection against recurrences.

The ablative fractional laser can be used to create channels of ablation into the epidermis and dermis and to facilitate penetration of the photosensitizing substance. The combined therapies of ablative fractional laser and PDT may allow a higher efficacy (18). Ablative fractional carbon dioxide laser was used to facilitate the action of 5% 5-FU, applied topical under oclusion on superficial BCCs and squamous cell carcinoma *in situ* on the trunk and extremities; the results showed 87% histologic clearance (21).

In 2013, Kim S.A. reported a combination of CO_2 laser ablation and topical MAL PDT, followed by modified cryotherapy that provided an effective method for the treatment of nodular and superficial BCC (22).

Discussions

The NCCN (National Comprehensive Cancer Network) 2016 guideline presents some conclusions regarding the superficial therapies for BCC: PDT has similar efficacy as cryotherapy, but better cosmetic outcomes and PDT, imiquimod and 5-FU have similar efficacy and cosmetic outcomes, with a lower risk of recurrence after imiquimod (7).

Also in 2016, the group lead by Roozeboom published the results of a follow-up study which concluded that according to results at three years post-treatment, imiquimod is superior and fluorouracil not inferior to MAL-PDT in treatment of superficial basal cell carcinoma (23).

The increasingly frequent use of noninvasive treatments for BCC leads to the need for effective, noninvasive diagnostic tools to assess the effectiveness of treatments and the appearance of recurrence.

A study published in 2014 in *British Journal of Dermatology* discusses the role of dermoscopy in

the evaluation of outcome and monitoring of sBCC after nonablative therapies.

The term of residual disease-associated dermoscopic criteria (RDADC) was introduced reffering to the presence of pigmented structures, ulceration and arborizing vessels (24). The results of this study indicate that RDADC are associated with residual disease and can accurately predict the presence of sBCC in histopathology, while the disappearance of tdermoscopic criteria of sBCC correlates well with complete clearance.

Digital imaging diagnostic techniques have emerged in the last years. *In vivo* reflectance confocal microscopy (RCM), multiphoton microscopy (MPT) and optical coherence tomography (OCT) are of use in the diagnosis of cutaneous tumors. RCM has the highest sensitivity and specificity confirmed in large studies (3).

Laser-induced fluorescence spectroscopy (LIF) represents a new diagnostic technique for the diagnosis and demarcation of BCC. LIF relies on the principle of differential fluorescence emission between abnormal and normal skin tissues (*ex vivo* and *in vivo*) in response to excitation by a specific wavelength of light. It is a noninvasive, high sensitive and user-friendly methodology (25).

Conclusion

In view of the many existing nonsurgical treatment options, the physician must choose the most appropriate method or methods that would best meet the goals of the patient. Nonsurgical therapies, such as topical creams and phototherapies, are superior to surgical therapies for non-advanced BCCs in cosmetically sensitive areas, however higher recurrence rates and longer treatment times should be explained to the patient and may be forseeable. Additionally, nonsurgical therapy is usually more effective for superficial BCCs than nodular BCCs. In cases of deep or infiltrating BCC, nonsurgical modalities should be used with caution and clinicians may want to consider a combination of therapies to minimize recurrence.

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