Different treatment options of basal cell carcinoma: between classic and recent modalities, Review article

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Abstract:
Basal cell carcinoma (BCC) is a common non melanoma skin cancer with rising incidence. Although with good prognosis, it has chronic and progressive course. Mohs surgery is the classic and gold standard treatment. Other lines which are less invasive and more practical are available such as radiotherapy, photodynamic therapy and topical therapy. These modalities are suitable especially in cases not candidate for surgery. In this paper we will discuss different classic and alternative lines of BCC treatment.
Introduction:
Basal cell carcinoma (BCC), it was called previously as basal cell epithelioma, is the most common non melanoma skin cancer. It mostly appears in sun-damaged skin. Basal cell carcinoma is usually a slow-growing with benign course, it can be destructive for vital structures as eye and bone and can be cosmetically disfiguring in visible sites when treatment is inadequate or delayed. On clinical examination, BCC usually appears as pink-colored papules with overlying ulceration or telangiectasia. BCC occurs on the head or neck in the majority of cases, but can involve the trunk and extremities. Most sporadic BCCs can be simply managed by surgical or non-surgical methods, but BCCs with high risk of recurrence need to be managed with more destructive methods. Hazard of local recurrences increases with tumor size, poorly defined edges, invasive histological subtype or with history of previous recurrences.

-Tumor risk stratification:
There are many available therapeutic lines for BCC management. The decision for surgical intervention of the BCC lesion depends on being low or high risk. BCC risk stratification depends on factors that can accelerate tumor recurrence, including location, size, borders, primary versus recurrent disease, histologic and host factors.

<table>
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<tr>
<th>Table 1: Risk factors for basal cell carcinoma recurrence (National Comprehensive Cancer Network Guidelines)</th>
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<tr>
<td><strong>Clinical presentation</strong></td>
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<td>-Location/size Area</td>
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<td><strong>Histopathology</strong></td>
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<td>-Histopathologic subtype</td>
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<td>-Perineural Involvement</td>
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**Area H**, “Mask areas” of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet; **Area L**, trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles); **Area M**, cheeks, forehead, scalp, neck, and pretibia.

**Low-risk histologic subtypes** include nodular, superficial, and other nonaggressive growth patterns, such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
High-risk histologic subtypes include morpheaform, basosquamous, sclerosing, infiltrative and micronodular

Prevention

1- Sun protection education
Limiting the exposure to UV radiation through avoiding direct exposure to the sun between 10:00 AM and 4:00 PM, wearing sun-protective clothing which are made from fabric labeled with UV protection factor (UPF), UV-protective sunglasses are also recommended, using a broad-spectrum sunscreen that protects against both UVA and UVB radiation. Avoiding tanning beds or tanning salons can lower the risk of developing skin non-melanoma cancer 6.

2- Chemoprevention
Topical use of tazarotene gel 0.1%, combined antioxidants (L-ascorbic acid (vitamin C) and vitamin E reduce the thymine dimer formation, in addition to sunburn cell formation, and upregulate matrix metalloproteinase-9 and p53, which are involved in the etiopathogenesis of BCC. Oral administration of difluoromethylornithine (a synthetic analog of the amino acid ornithine) over 4-5 years can reduce BCC. Products like beta-carotene, polyphenols (either systemic or topical), statins, oral retinoids and NSAIDs also can be used as chemoprevention 7.

- Tazarotene
Tazarotene is a topical retinoid with relative specificity for RAR-β and RAR-γ (Retinoic acid receptor) so improve epidermal differentiation and proliferation. It is suggested that tazarotene inhibition of PI3K/Akt signaling is an important mechanism for chemoprevention (So et al., 2008). It can replace oral retinoids as it specifically activate RARγ in the normal skin and in BCCs, so can reduce the side effects associated with using systemic retinoids. It only may induce slight skin irritation and erythema. Tazarotene can decrease tumor burden of BCC and also can treat small lesions 8.

- NSAIDs (non-steroidal anti-inflammatory drugs)
NSAIDs has a potential role in the chemoprevention of non-melanoma skin cancers (NMSC) including BCC and SCC 9. The suggested mechanism of NSAIDs induced chemoprevention is the inhibition of cyclooxygenase (COX) enzymes and the subsequent decrease in prostaglandin synthesis. Unlike the COX-1 isoenzyme, which is heavily expressed in the normal skin, the COX-2 isoenzyme is usually undetectable in normal skin, but upregulated by ultraviolet radiation (UVR). COX-2 upregulation in a heavily UVR exposed skin can induce cell proliferation, angiogenesis, and suppression of apoptosis then carcinogenesis 10.

- Oral Retinoids
Retinoid chemoprevention is suggested to be effective in certain patient populations as Xerodermia pigmentosa and Neviod BCC syndrome. The long-term monitoring of skeletal system with X-ray imaging is mandatory as prolonged use of systemic retinoids can cause calcification of tendons and ligaments, hyperostosis of the spine and rarely osteoporosis 11.

Treatment

1- Surgical modalities
Mohs surgery is considered the most effective technique for treating many basal cell carcinomas (BCCs). Sometimes called Mohs micrographic surgery, the procedure is done in stages, including lab work, while the patient waits. This allows the removal of all cancerous cells for the highest cure rate while sparing healthy tissue and leaving the smallest possible scar.  

- Excisional surgery is a very effective therapeutic option for primary BCC treatment, with recurrence rates varying from 2% to 8% at 5 years after operation. Current recommendations suggest a range of safety margins between 2 mm and 5 mm in low-risk tumors and between 5 mm and 15 mm in high-risk lesions.

2- Non-surgical modalities

Non-surgical destructive modalities including topical treatments or photodynamic therapy (PDT), either alone or combined, may be used for low-risk BCCs when surgery is contraindicated or not applicable.

A-Topical treatment

- Imiquimod

Imiquimod acts as an immune response modifier by binding to toll-like receptors (TLR) 7 and 8 of macrophages, monocytes, and dendritic cells, activation of TLRs leads to stimulation of a cascade of intracellular pathways that finally produce nuclear factor-kappa B (NF-κB). This NF-κB leads to induction of proinflammatory cytokines such as interleukin-1, tumor necrosis factor-α, interferon-α (IFN-α), and IFN-β. It is approved in Europe and the USA for the treatment of small BCCs in immunocompetent adults.

Imiquimod exerts its effect in BCC via three different mechanisms – production of proinflammatory cytokines, augmentation of adenosine receptor-associated inflammation, and direct proapoptotic activity, which finally induce inflammation that leads to resolution of the lesion.

The recommended dosing schedule in the USA and Europe is 5 times a week for 6 weeks with success rate of 73–77%. The most common adverse effects of imiquimod are erythema, scaling, ulceration and flu-like symptoms.

5-  Flurouracil

Topical Flurouracil 5% formulation acts as antimetabolite induces cellular death in cells with high mitotic activity and decrease DNA synthesis in the neoplastic cells, leading to decreased cell proliferation and promoting apoptosis.

It is approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of small low-risk BCC. The recommended regimen is two applications per day, for about 11 weeks with an average of a three-week period of follow-up. It gives good cosmetic outcome, no scarring and only slight erythema.

B- Destructive therapies

Destructive therapies with curettage, electrocautery (electro-desiccation), cryotherapy and laser ablation are therapeutic options for small, low-risk non-facial BCC and for multiple small BCCs. Curettage allows histopathological assessment, which is not possible with cryotherapy or laser ablation because of tissue destruction.

Intralesional cryotherapy is safe, non-toxic, well-tolerated and would seem to achieve good results in a high proportion of patients. CO₂ and erbium yttrium aluminium garnet
(Er:YAG) lasers ablate tissue through the vaporization of tissue water, either in full ablative or fractional mode. Tissue interaction and efficacy rates relays on the used parameters.

C- Photodynamic therapy
PDT with photosensitizer 5-aminolevulinic acid (ALA) or its methyl ester (methyl-5-amino-4-oxopentanoate, MAL) considered as an effective therapeutic option in patients with non aggressive, low-risk BCC, i.e. small superficial and nodular types, not exceeding 2 mm thickness, when surgery is not suitable or contraindicated. PDT acts through interaction between the photosensitizer and a specific wavelength of light in the presence of oxygen producing reactive oxygen species specially singlet oxygen which result in lesion ischemic necrosis with or without apoptosis.

Combined therapies can be considered in patients not suitable for standard treatment. CO₂, Er:YAG (Erbium yttrium aluminium garnet), diode lasers or partial surgical debulking before PDT have shown cure rates of 92.9-98.9% in BCC, which is higher cure rate than each method separately with mild side effect such as hypopigmentation.

D- Radiotherapy
Different types of local Radiotherapy (RT) are suitable as an alternative to surgical treatment of BCC. These include superficial RT, conventional RT with electron beams and brachytherapy. Due to presence of long term side effects of RT as increase incidence of future malignancies, primary RT is recommended only in patients above the age of 60 years who are not amenable to or refuse surgery.

E- Other lines

Chemotherapeutic Agents
Before the era of molecular target therapies, metastatic BCC had been managed with various traditional cytotoxic chemotherapies, especially Platinum containing regimens.

Molecular Targeting Agents
Two molecular targeting agents, i.e., vismodegib and sonidegib, are currently used for treatment of advanced BCC which were approved by the FDA. Both are oral small molecule inhibitors of SMO, which block HH signaling activation. The antifungal drug, itraconazole, has also been reported to inhibit HH signaling activity by acting on SMO. Statins and vitamin D in high doses also reported to inhibit SMO and inhibit BCC proliferation.

- Vismodegib and Sonidegib
Vismodegib is a small-molecule inhibitor of SMO that selectively inhibits the HH signaling pathway by binding to the drug-binding site of SMO. It is derived from a naturally occurring alkaloid, cyclopamine. Both vismodegib and sonidegib can induce chemotaxis of cytotoxic T cells into the BCC environment and upregulate major histocompatibility (MHC) class I in BCC cells. That's why they produce synergistic effect when given with immune modifiers.

They give better response in younger patient, with no previous chemotherapy, had Gorlin’s syndrome, or had smaller tumors (≤ 4 cm). The efficacy of the treatment was...
equal for aggressive and non-aggressive histological subtypes. Few reported side
effects as muscle spasm, alopecia, nausea and vomiting, fatigue and weight loss. Dosing of vismodegib at 150 mg 3 times per week, the dose based on maximal plasma concentration and pharmacodynamic response. Vismodegib has been shown to reduce tumor burden and decrease recurrence after discontinuation of therapy. It can be used as neoadjuvant treatment prior to surgery, which reduce the extent of surgical treatment. Sonidegib is available as an orally administered or topical 0.75% cream for the treatment of BCC. Oral sonidegib dose is 200 mg daily and sonidegib 0.75% cream applied twice daily for 4 weeks.

Immunotherapy
It has been found that BCCs have the highest mutational burden of all human cancers. As mutational burden is a known predictor of response to cancer immunotherapy. So immunotherapy as PD-1 inhibitors (programmed cell death inhibitors) is proposed to treat advanced BCC. Topical imiquimod also considered a topical immunotherapy. It acts as immune response modifier inducing inflammation that leads to resolution of the lesion.

Topical SMO inhibitor
Cyclopamine, the teratogenic steroidal plant alkaloid, which was topically applied, succeeded already to induce regression of four sporadic BCCs.

Inhibitors of the GLI transcription
Two tested candidates GANT58 and GANT61, possibly provide a therapeutic option.

Tyrosine kinase inhibitors
Sorafenib or imatinib, can be used because PDGFRα is supposed to mediate downstream effects in HH signaling.

Intralesional chemotherapy Injection in BCC
Side effects of systemic therapy and the risks and consequences of surgery push scientists to find new therapeutic options for treating cutaneous malignancy. Intralesional drug delivery allow for local delivery of potent chemotherapeutic drugs, avoiding systemic toxicity and surgical complications. Management of cutaneous malignancy with intralesionally injected agents is an area worthy of further researches. Intralesional chemotherapy for non-melanoma skin cancer is available for more than 5 decades. Unfortunately it is not commonly used modality. Barriers to its use include the absence of therapeutic guidelines, off-label utilization of these agents, a relatively small number of patients treated, and a lack of large, well-designed trials with long-term follow-up. Intralesional 5-fluorouracil is a potentially affordable option in BCC that was used for many years ago with good efficacy and minimal adverse effects.

Intralesional MTX, as an example of a nonsurgical treatment modality for BCC, offers a less invasive treatment option with acceptable cosmetic results. On the other hand, this approach could constitute a neoadjuvant therapy to reduce tumor size while waiting for surgery to reduce surgical invasiveness.
References


