Basal Cell Carcinoma

Subjects: Oncology

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Basal cell carcinoma (BCC) is the most common human cancer worldwide, and is a subtype of nonmelanoma skin cancer, characterized by a constantly increasing incidence due to an aging population and widespread sun exposure. Although the mortality from BCC is negligible, this tumor can be associated with significant morbidity and cost.

basal cell carcinoma, skin cancer, skin tumour

1. Introduction

The incidence of nonmelanoma skin cancers (NMSC), which include basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), and actinic keratosis (AK), is increasing worldwide. BCC is the most frequent skin cancer, with constantly increasing incidence due to an aging population and widespread sun exposure. BCC accounts for 50% of all cancers in the United States [1]. Although the mortality from this cancer is negligible, BCC can be associated with significant morbidity, especially if the tumor is untreated for a long period of time [2]. Clinically, it presents with several morphologies and the clinical differential diagnosis should take into consideration a broad variety of diseases ranging from benign lesions to melanoma. Dermoscopy, and, more recently, reflectance confocal microscopy (RCM) have largely improved BCC diagnosis. Several effective therapeutic approaches are available to treat BCC, and an appropriate selection requires knowledge of complications, cosmetic outcomes, and recurrence rates. Additionally, patient's preferences, of course, must be explored and included in the therapeutic decision. Surgery remains the first-line treatment for this disease. The pathogenesis of BCC depends on the interplay between environmental factors and genetic features of the patient. Aberrant activation of Hedgehog signaling is a driver of BCC development, and its blockade represents a potential therapeutic target. Therefore, Hedgehog pathway inhibitor therapy is emerging as a useful targeted treatment for patients with local advanced or metastatic BCC. Moreover, the implementation of prevention measures may play a crucial role in the improvement of BCC management.

2. Treatment of Localized BCC

The primary goal for the treatment of localized BCC is the complete excision of the skin tumor and the preservation of the cosmetic and functional aspects. Therefore, surgery is the most common treatment for localized BCC. Traditional approaches like curettage or electrodessication are supported by older studies including prospective

trials with limited follow-up time. Other techniques are discussed below. According to one evidence-based review, the best results have been obtained with surgery [3].

2.1. Surgery

The National Comprehensive Cancer Network (NCCN) recommends clinical margins of at least 4-mm for low-risk BCC treated with standard excision with postoperative margin assessment (SEPMA) [4]. The results of Wolf et al. showed that, for well-circumscribed BCC < 2-mm in diameter, excision with 4-mm clinical margins guarantees a complete removal in more than 95% of cases [5]. In a retrospective study on 3957 consecutive excisions of BCC, primary tumors of any size on the neck, trunk, and extremities had a 5-year cure rate > 95% [6]. If SEPMA is utilized for high-risk BCC, wider surgical margins (more than 6 mm) than those reported for low-risk BCC are necessary, and greater recurrence rates of this tumor should be expected [4].

2.2. Mohs Micrographic Surgery (MMS)

MMS, or Mohs surgery, is a surgical procedure in which the complete excision of the NMSC is examined by microscopic margin control. MMS is the treatment of choice for high-risk and recurrent BCCs showing superior long-term cure rates than other surgical treatments. MMS allows intraoperative analysis of 100% of excision margin. Rowe et al. reported that the 5-year recurrence rates for primary and recurrent BCCs treated with MMS are 1% and 5.6%, respectively, compared with 10.1% and 17.4%, respectively, for SEPMA [7]. Likewise, the 10-year recurrence rates for primary facial BCCs were 4.4% for MMS and 12.2% for SEPMA [8]. The excision with complete circumferential peripheral and deep margin assessment (CCPDMA), using intraoperative frozen section assessment, is a valid alternative to MMS because it includes an entire assessment of all deep and peripheral margins [4].

2.3. Curettage and Electrodessication

Curettage and electrodessication is a fast and cost-effective technique for superficial lesions and recommended by the NCCN for properly selected and low-risk BCCs. However, these techniques do not allow for histologic margin assessment [4]. It has to be considered that these techniques should be avoided in areas with terminal hair growth such as the scalp, pubis, axillae, or the beard area in males, due to the risk of follicular tumor extension. Silverman et al. reported in a study of more than 2300 BCCs a 5-year recurrence rate of 3.3% (standard error [SE]: 1.5%) for lesions of any diameter localized in the L area (trunk and extremities, excluding hands, nail units, pretibia, ankles, and feet). Lesions in the M area (cheeks, forehead, scalp, neck, and pretibia), had a 5-year recurrence rate of 5.3% (SE: 2.7%) and 22.7% (SE: 7.2%), for BCCs with diameters < 10 mm or >10 mm, respectively. For BCCs in the H area (“mask areas” of the face, genitalia, hands, and feet), the 5-year recurrence rates were 4.5% (SE: 2.6%) and 17.6% (SE: 5.4%) for BCC < 6 mm or >6 mm, respectively [9].

2.4. Cryosurgery

Cryosurgery destroys tumor cells by freeze–thaw cycles. It is a fast and cost-effective technique but lacks histological assessment of tumor margins. Even if several large case series report cure rates of 94%–99%, this technique should be limited to superficial and low-risk BCCs [10]. As demonstrated by prospective randomized trials, a drawback of cryotherapy is the poorer cosmetic result compared to other treatment approaches [11].

2.5. Photodynamic Therapy (PDT)

PDT consists in the application of a photosensitizing agent, generally aminolevulinic acid (ALA), or methyl aminolevulinate (MAL), followed by irradiation with a light source. Cure rates range from 70% to 90% but it has to be considered that the reported studies have short follow-up periods [12]. Roozeboom et al. reported a 5-year recurrence rate of 30.7% (95% CI, 21.5–42.6%) for ALA-PDT and 2.3% (95% CI, 0.6–8.8%) for surgical excision ($p < 0.0001$) [13]. When stratifying for tumor thickness, the ALA-PDT cure rate was 95% for primary thin NBCCs (i.e., thickness ≤ 0.7-mm) [13]. Most articles on PDT for BCC showed high cure rates for the superficial and nodular subtype of this tumor [14][15]. Considering the nodular subtypes, cure rates are better for thinner forms [13]. Therefore, this technique should be considered mainly for superficial BCCs and for thinner nodular subtype, generally in patients affected by extensive or multifocal disease, or with multiple AKs.

2.6. Radiation (RT)

RT is a primary therapy indicated in patients where surgery is contraindicated or for unresectable tumors. The goal of RT is a complete eradication of the BCC with preservation of the healthy tissue. Two types of RT have been utilized for the treatment of BCC, i.e., teletherapy (external beam RT) and brachytherapy [16]. RT is mainly used in patients over 60 years of age but it is contraindicated in patients affected by genetic syndromes, like BCNS or Gorlin–Goltz syndrome, due to the higher risk to induce other malignancies caused by ionizing radiation [17].

RT has been compared with many other treatments for BCC in prospective RCTs. Hall et al. compared cryotherapy with superficial RT in 93 patients evaluated 2 years after treatment, reporting a 4% recurrence of the disease after RT, compared to 39% after cryotherapy [18].

Avril et al. compared RT to surgery in newly diagnosed facial BCCs. Most RT patients (55%) were treated with low dose rate interstitial brachytherapy (*n*: 173) while others (12%) received conventional outpatient teletherapy. Recurrence ≤ 4 years after treatment occurred in 0.7% of the surgery group and 7.5% of the RT group (8.8% after brachytherapy, 5% after teletherapy) [19].

2.7. Topical Therapies

Topical 5-fluorouracil (5-FU) 5% cream, and imiquimod 5% cream are approved for the treatment of superficial BCC [20][21][22][23][24]. In an RCT that used twice daily imiquimod 5% for 12 weeks, Geisse et al. reported a 100% histologic clearance after 6 weeks of treatment [21] Other studies reported clearance rates of 77.9% and 80.4% for superficial BCC at a 5-year follow-up [25][26]. NBCCs showed similar results, with a 76% clinical clearance using

once daily imiquimod application for 12 weeks [27]. Imiquimod 5% is also utilized for patients affected by BCNS [28] [29].

An RCT showed a statistically equivalent efficacy between 5-FU and imiquimod 5% in treating superficial BCC at a 12-month follow-up [30]. Other studies with longer follow-up showed a superiority of imiquimod, with a 79.7% clearance rate at 3 years compared with 68.2% for 5-FU [31]. 5-FU is not recommended for NBCC, and evidence of its efficacy in this subtype is limited to case reports [32][33].

Topical treatments may be responsible for adverse side effects, such as erythema, swelling, and erosions, thus limiting compliance and hampering effectiveness. The use of these treatments should be limited to superficial BCCs or small BCCs localized in low-risk areas that could not be treated with other regimens [34].

2.8. Intralesional Therapy

Several intralesional chemotherapies have been tested for BCC treatment, such as 5-FU, interferons, interleukin-2, and bleomycin, with uneven results. Adverse events are unusual, generally dose dependent, and include local effects at the treatment site and flu-like symptoms [16][35].

2.9. Laser Therapy

Laser therapy has been studied for BCC treatment as both monotherapy and adjunct therapy [36]. Campolmi et al. reported a 100% histologic clearance and no recurrences over a 3-year follow-up period for superficial and NBCC treated with superpulsed carbon dioxide laser therapy [37][38]. In a retrospective study of 2719 facial BCCs treated with pulsed neodymium-based laser therapy, Moskalik et al. reported a recurrence rate of 1.8% for follow-up times ranging from 3 months to 5 years [39]. Adverse effects reported with laser therapy were reactive hyperemia, edema, scarring, and soreness [36].

3. BCC Prevention

Although early diagnosis and prompt treatment are indispensable means to improve BCC outcomes, the implementation of prevention measures may play a crucial role, especially if these are applied in childhood and adolescence.

Prevention consists of lifestyle changes such as avoiding sunburns, tanning beds, and prolonged direct sun exposure between 10 a.m. and 4 p.m., as well as shade seeking, sunscreens application on the skin, physical barrier methods such as protective clothing, hats, and sunglasses. Preventive action should also be recommended for widespread professional UV exposure among outdoor workers [40]. Regular sunscreen use in childhood and adolescence seems more beneficial than in adulthood [41]. All these are practical indications that are not yet supported by high quality studies [42].

Continued long-term surveillance of these patients is also essential. The NCCN Guidelines recommend a whole-body skin examination every 6–12 months for the first 2 years after BCC diagnosis, and then at least annually for life [43]. However, patients are encouraged to practice active self-monitoring.

To date, BCC prevention includes the oral intake of a water-soluble vitamin B3 derivative, Nicotinamide (NAM), which is a component of foods like meat, fish, legumes, mushrooms, nuts, and grains [44]. It derives from tryptophan metabolism too, which accounts for 50% of its synthesis [45]. It is metabolized by the liver and secreted by the kidneys [46]. Nicotinamide plays a key role in the glycolysis pathway, producing NAD+ for ATP production to maintain cellular energy and sustain metabolic steps [47]. NAM deficiency, or pellagra, which targets organs with high cellular energy requirements, is characterized by photosensitive dermatitis, diarrhea, and dementia [45][47]. NAM-mediated photoprotection and skin cancer chemoprevention were studied at first in mice by Gensler et al. in 1997 and 1999 [48][49]. They found that topical and oral NAM prevented UV-induced immune suppression and tumor formation [48][49]. Subsequently, Damian et al. demonstrated similar effects in reducing UV immune suppression [50] and the development of NMSCs in Australian patients [51]. NAM is involved in preventing keratinocyte damage, and consequently skin cancer, by influencing several processes such as reduction of DNA damage and optimization of DNA damage response. NAM enhances the ATP-mediated repair of UV-induced DNA damage, and thus reduces both mutation rate and UV-induced immune suppression [52]. Moreover, NAM reduces UV-induced inflammation downregulating IL-6, IL-10, MCP-1, and TNF-α. NAM is considered a cutaneous immunity normalizer as counteracts UV-induced immune suppression [53]. All these beneficial actions may reduce aging-related skin changes [52] and NMSC incidence [51][54][55][56]. However, continuous NAM administration is needed to maintain its photoprotective effects [53].

In two double-blind, randomized, placebo-controlled phase two trials in Australians with sun-damaged skin and an average of more than 30 AKs at baseline, oral NAM was administered at doses of 500 mg twice daily and 500 mg once daily. Relative reductions in AK of 35% and 29% with twice daily and once daily NAM dosing have been reported, respectively, within 4 months [54]. A phase III randomized controlled trial (ONTRAC) was led on 386 Australians with a history of at least two NMSCs during the previous five years. The study showed that oral NAM (500 mg twice daily for 12 months) is safe and effective in reducing the rates of new NMSCs and AKs. The rate of new NMSCs was lower in the NAM group than in the placebo group (relative rate reduction, 23%; $p = 0.02$). Similar ranges of reduction were found for both BCC (relative rate reduction 20%, $p = 0.120$) and SCC (relative rate reduction 30%, $p = 0.050$) [51]. In addition, two small phase II randomized controlled trials showed that NAM may also obtain a chemopreventive and curative action in immune-suppressed transplant recipients. Thirty renal transplant recipients received placebo or nicotinamide 250 mg thrice daily for six months and reported reductions in AKs size and count without detectable effects on the blood levels of the immunosuppressive drugs regularly received by the patients [55]. Finally, 22 renal transplant recipients were treated with placebo or NAM 500 mg twice daily for 6 months and nonsignificant trends to reduction in new skin cancers and AKs were found, without significant increase in AEs nor significant change in blood parameters or blood pressure [56]. Therefore NAM (500 mg twice daily) should be considered a valid option for the BCC prevention, especially the secondary prevention in high risk patients with pre-existing BCC.

Systemic retinoids slow down the cell cycle and promote antitumor effects through a more efficient cellular repair of UV-induced damage [57]. They have been used as chemopreventive agents in the genetic syndromes and immunosuppressed patients. However, they displayed chemopreventive action for SCC and not for BCC [16].

Other studies suggest that pharmacological inhibition of COX-2 may hamper epithelial neoplasms, and that daily use of celecoxib might reduce the risk of developing BCC [58][59]. High-risk patients with a positive history of past BCC seem to take advantage from celecoxib treatment. However, there is poor evidence in the literature and the results are too conflicting to recommend it for chemoprevention [57].

PDT reduces the number of new cases of AK whereas it has not a clear chemopreventive effect on NMSC [60]. Only a case report on a patient with BCNS indicates that MAL-PDT to be an effective chemopreventive agent against new BCC development. However, these results need to be validated in larger studies [61].

The dietary supplements of β-carotene and selenium have also been studied, but they did not display a chemopreventive action against BCC or SCC in patients with a history of BCC [62].

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