Basal Cell Carcinoma Management

Mohamed Hamed Khater [1], Aya Raafat Abdulkhalik Sayed Ahmed[2], Al Shimaa Mohamed Ibrahim[3]

1 Professor of Dermatology, Venereology, and Andrology, Faculty of Medicine, Zagazig university

2 MBBCH, Faculty of Medicine, Zagazig University

3 Assistant Professor of Dermatology, Venereology, and Andrology, Faculty of Medicine, Zagazig university

Abstract

Background: *Cutaneous basal cell carcinoma is the most common cancer in White people. It is so named because the cells of basal cell carcinoma resemble the cells of the basal cell layer of the epithelium. Cutaneous basal cell carcinoma affects mainly chronically sun-exposed skin of the head and neck of fair complexioned older people. Both intermittent acute, and long-standing continual exposure to UV are high risk factors for cutaneous basal cell carcinoma. It is a slow-growing cancer that if left untreated will invade locally, but only rarely metastasizes. Black people are rarely affected. Patients with basal cell carcinoma syndrome should not be treated with ionizing radiation.Alternative treatment procedures – for multiple or superficial basal cell carcinomas, and in inoperable patients – as locally destructive procedures (electrodesiccation, curettage, cryotherapy, laser therapy, and photodynamic therapy as well as local drug treatments with imiquimod may be considered. Until approved, systemic treatment with Hedgehog inhibitors should be considered in the framework of clinical trials for selected patients with inoperable or metastatic basal cell carcinoma. Human papillomavirus (HPV) vaccines are among the most effective prophylactic vaccines available and have established several important landmarks in human vaccinology. Human papillomavirus (HPV) vaccines, which were introduced in many countries in the past decade, have shown promising results in decreasing HPV infection and related cutaneous and/or mucosal disease including cutaneous and genital warts, nonmelanoma skin cancer, and recurrent respiratory papillomatosis RRP, as well as for cervical, anal, and vulvar dysplasia.*

Keywords: *Basal Cell Carcinoma, Human Papillomavirus Vaccine*

Introduction

Cutaneous basal cell carcinoma is the most common cancer in White people. It is so named because the cells of basal cell carcinoma resemble the cells of the basal cell layer of the epithelium. Cutaneous basal cell carcinoma affects mainly chronically sun-exposed skin of the head and neck of fair complexioned older people. Both intermittent acute, and long-standing continual exposure to UV are high risk factors for cutaneous basal cell carcinoma. It is a slow-growing cancer that if left untreated will invade locally, but only rarely metastasizes. Black people are rarely affected [1].

Clinical manifestations are various papulonodular lesions with a pearl transparent rim, destructive ulcerative lesions called ulcus rodens, pale foci with various degrees of induration, erythematous foci with obvious telangiectasia, or cystic nodules. BCCs may have varying sizes.

Lesions of a few millimeters can already be identified and, as they develop reaching up to several centimeters, clinical features become more evident In most cases the clinical diagnosis is not difficult for an experienced clinician. There are cases, however, when the final diagnosis may be determined only on the basis of a histological examination of a completely removed tumour [1].

Guidelines of care for the management of basal cell carcinoma

The National Comprehensive Cancer Network (NCCN) guidelines define clinical and pathological risk factors for the recurrence of BCCs [1]. Clinical risk factors are immunosuppression, prior radiotherapy of the tumor lesion, a recurrent tumor, poor border clarity, a tumor of any size in high-risk areas (central face, eyelids, eyebrows, periorbital area, nose, lips, chin, mandible, preauricular and postauricular skin, temple, ear, as well as the genitalia, hands, and feet), a tumor with a major axis ≥ 10 mm in medium-risk areas (cheeks, forehead, scalp, neck, and pretibia), and a tumor with a major axis ≥ 20 mm in low-risk areas (trunk and extremities, excluding the pretibia, hands, feet, nails, and ankles). Pathological risk factors are perineural involvement and a morpheaform, basosquamous, micronodular, or mixed infiltrative subtype [1].

▪ Surgical treatment with histological control of the complete removal of the tumor with no remaining cells at the resection margins should be offered as the first-line therapy. Surgery may be done with systematic control of the margins (micro-scopically controlled surgery) or with a tumor-adapted safety margin and conventional histologic examination. For superficial basal cell carcinomas, horizontal excision (shave excision) with conventional histology is also possible.

▪ For local tumors that cannot be removed, as well as for inoperable patients, an interdisciplinary treatment concept is warranted. Usually, radiation treatment is performed in such situations.

▪ Patients with basal cell carcinoma syndrome should not be treated with ionizing radiation.

▪ Alternative treatment procedures – for multiple or superficial basal cell carcinomas, and in inoperable patients – as locally destructive procedures (electrodesiccation, curettage, cryotherapy, laser therapy, and photodynamic therapy as well as local drug treatments with imiquimod or 5-fluorouracil) may be considered.

▪ Until approved, systemic treatment with Hedgehog inhibitors (Vismodegib, LDE225) should be considered in the framework of clinical trials for selected patients with inoperable or metastatic basal cell carcinoma [2].

▪ Nonsurgical Treatment

In general, treatment of BCC is most effectively accomplished by surgical therapy. There are relatively few exceptions to this guiding principle. If surgical therapy is not feasible or preferred, cryosurgery, topical therapy (eg, imiquimod or 5-fluorouracil [5-FU]), photodynamic therapy PDT (with aminolevulinic acid [ALA] or methyl aminolevulinate [MAL]), or radiation therapy and Laser therapy for BCC can be considered when tumors are low risk, with the understanding that the cure rate may be lower [3, 4].

5-fluorouracil

Topical 5-FU decreases cell proliferation and induces cellular death, particularly in cells with high mitotic rates, through inhibition of thymidylate synthetase, which interferes with DNA synthesis. Evidence suggests that 5-FU used as a topical chemotherapeutic agent in Nonmelanoma Skin Cancer (NMSC) has been effective for the treatment of superficial BCC (sBCC) [5].

Imiquimod

Imidazoquinoline amineis is a synthetic immune modulator, stimulating excretion of cytokines such as IFN-alpha, IL-6, and TNF-alpha. Imiquimod is indicated for single primary superficial BCC, sized from 0.5 to 2 cm diameter. It is not applied in the area of the eyes, nose, lips, and cochlea. The efficacy of 6 weeks imiquimod treatment of BCC varies from 70 to 94% [4].

Laser treatment

It is suitable for treatment of superficial BCC. CO2 laser succeeded complete clearance after one treatment in more than 80% of BCC patients. The recurrence rate after ablative laser therapy varies between 3.7 and 15.5% [4].

Photodynamic therapy (PDT)

Photodynamic therapy is based on the application of a photosensitizer to the tumor lesion followed by illumination of the lesion with visible light, resulting in subsequent selective tumor cell death. The therapeutic protocol usually consists of two sessions 1 week apart, which may be repeated in cases of incomplete clinical response. Superficial lesions are the most responsive to this treatment modality, which usually results in excellent or good aesthetic results [6].

Cryosurgery

Cryosurgery uses freeze-thaw cycles in order to destroy the malignant tumor cells, and, as with curettage and electrodes-sication, does not allow the microscopic examination of tumor margins and is mostly recommended in low-risk cases [5].

Hedgehog pathway inhibitors

Hedgehog pathway inhibitors, such as Vismodegib, are used in surgically advanced tumors as neoadjuvant therapy, prior to Mohs micrographic surgery or radiotherapy, allowing the tumor to decrease in size. As is the case with other treatment agents, its long-term use is associated with adverse effects and in order to combat such effects, treatment interruptions of up to 8 weeks have been practiced [5].

Radiation therapy

The advantage of RT is that it spares structures of cosmetic or functional importance. Reported overall 5-year cure rates are 91–93% for previously untreated BCCs and 86–91% for recurrent BCCs. However, BCCs that recur following RT may behave more aggressively, including a second recurrence and distant metastasis. In addition, although evidence regarding the long-term efficacy of RT is limited, delayed side effects within the treatment field, such as chronic radiation dermatitis, permanent alopecia, dermal and subcutaneous fibrosis, necrosis, and secondary cutaneous malignancies, have been reported. Furthermore, the favorable cosmetic results may deteriorate with time [1, 7]. RT is, therefore, generally reserved for patients ineligible for surgical therapy, particular those with tumors in high-risk areas [1].

Treatment of locally advanced and metastatic BCCs

The metastasis of BCCs usually occurs in association with deeply invasive lesions or those 9-10 cm2 in diameter. The estimated rate of BCC metastasis ranges from 0.0029 to 0.55%, with regional lymph nodes, lungs, bones, skin, and liver as common metastatic sites. The prognosis of patients with metastatic BCC (mBCC) is poor. A literature review of 194 published cases reported a median survival time of 10.0 months (range: 0.5–108.0 months) after detection of the metastasis. However, these data were mainly those of patients treated with conventional multidisciplinary therapies, whereas a determination of the prognosis of patients treated with emerging therapies, such as SMO inhibitors, awaits further investigation [1].

PREVENTION

Excessive exposure to ultraviolet radiation (UVR) during childhood and adolescence has been associated with an increased risk of melanoma, basal cell carcinoma, and squamous cell

carcinoma. Common risk factors for all three tumor entities include sun exposure and DNA-repair deficiencies [8].

Since solar UV irradiation represents the most important environmental risk factor for the development of skin cancer, skin protection against UV exposure is a fundamental part of cancer prevention. Approaches commonly used in order to prevent skin cancer include avoiding direct exposure to midday sun (between the hours of 10 am and 4 pm), [9] sunscreen was the most frequently recommended strategy to reduce sun exposure [8].

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 [10].

Human papillomavirus vaccines

Human papillomavirus.

HPV is a highly contagious, non-enveloped, double-stranded DNA virus transmitted via skin contact, vertical transmission, and fomites [11]. It affects mucosal and cutaneous tissues, causing cancers and neoplastic lesions, responsible for 5% of global cancers [12]. High-risk types (e.g., HPV16, HPV18) contribute to cervical, anal, and vulvar dysplasia, with HPV16 linked to SCC and HPV18 to adenocarcinoma and adenosquamous carcinoma [13-15].

In skin cancers, HPV's role in SCC and BCC is unclear, but beta HPVs may inhibit DNA repair and apoptosis post-UV exposure [15]. Up to 90% of SCCs in immunocompromised patients and 50% in immunocompetent individuals show beta HPV seropositivity, suggesting a potential etiologic link [16].

Human papillomavirus vaccine

Although surgery remains the standard of care for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), for patients who are poor surgical candidates, have multiple lesions, or defer surgery, alternative treatments are limited. Recent evidence suggests that the human papillomavirus (HPV) is involved in the pathogenesis of NMSC especially SCC [17].

Human papillomavirus (HPV) vaccines are among the most effective prophylactic vaccines available and have established several important landmarks in human vaccinology [12].

Types of vaccine:

Quadrivalent HPV vaccine, Gardasil (Merck & Co., Kenilworth, NJ, USA), is the first commercially available HPV vaccine licensed by the United States Food and Drug Administration (FDA), in 2006. The bivalent HPV vaccine, Cervarix (GSK, Brentford, UK) was approved by the European Medicines Agency (EMA) in 2007 and by the FDA in 2009. Cervarix protects against the most common oncogenic genotypes of HPV (types 16 and 18), which cause around 70% of cervical cancers. Gardasil, in addition to HPV16 and 18, also targets HPV6 and 11, which cause around 90% of genital warts. In 2014, a nine-valent vaccine, Gardasil 9 (Merck & Co., Kenilworth, NJ, USA), was licensed by the FDA, which offers protection against HPV6, 11, 16, 18, 31, 33, 45, 53, and 58. The five additional types covered by Gardasil 9 could cover HPV types related to another 20% of cervical cancer cases; thus, Gardasil 9 has the potential to protect against approximately 90% of cervical cancers [18].

Uses in dermatology

HPV vaccines, introduced in the past decade, have significantly reduced HPV infections and related diseases, including genital warts, nonmelanoma skin cancer (NMSC), recurrent

respiratory papillomatosis (RRP), and cervical, anal, and vulvar dysplasia [15, 13]. Current HPV-related treatments rely on physical destruction, which can cause discomfort, scarring, or depigmentation. The quadrivalent HPV vaccine, administered in a 3-dose schedule, has shown therapeutic efficacy for cutaneous warts and SCC/BCC [13].

Epidemiologic studies suggest an association between beta-HPV and NMSC, with beta-HPV positivity linked to SCC development [15]. Beta-HPVs, along with UV exposure, play a role in keratinocyte carcinogenesis, particularly in immunosuppressed transplant recipients. While current vaccines (Cervarix®, Gardasil®, Gardasil-9®) target alpha-HPVs affecting mucosal tissues, there is anecdotal evidence that they may also aid in the regression of cutaneous warts and cSCCs due to similarities in the L1 and L2 capsid proteins between alpha- and beta-HPVs [19].

HPV vaccines can be used therapeutically in different cases as shown below:

• Cutaneous warts.

Patients with cutaneous warts located on the hands, knees, feet, sole, chin, face, lips, tongue, and buccal mucosae treated by (quadrivalent vaccine, bivalent vaccine, nonavalent vaccine, and an unspecified vaccine) were given in the standard three dose series. More than 74 % of reported patients in study held by [13] experienced a significant decrease in the number of lesions after vaccination. particularly after receiving the quadrivalent vaccine.

• Genital warts.

HPV vaccination demonstrated an overall positive response. A study has done by [13] reported that 55.4% Of the reported patients who received an HPV vaccine had complete regression of warts.

• Nonmelanoma skin cancer.

There are 3 published reports on patients with SCC or BCC treated with three-dose series HPV quadrivalent or nonavalent vaccine. All of the patients demonstrated successful clinical regression [13]

The current literature demonstrates that HPV vaccination has expanded off-label as a therapeutic agent for HPV-associated cutaneous and mucosal conditions. Studies support the use of the commercially available three-dose series quadrivalent HPV vaccine to treat conditions such as cutaneous warts, nonmelanoma skin cancers, epidermodysplasia verruciformis, and recurrent respiratory papillomatosis. Various noncommercial HPV vaccines have demonstrated clinical improvement when used for the treatment of anogenital warts [13].

Mechanism of action

The mechanism of HPV vaccine involves virus-induced inhibition of DNA repair and apoptosis after ultraviolet radiation – induced DNA damage [15]. Currently, the licensed HPV vaccines are developed based on a virus-like particle (VLP) of the major papillomavirus capsid protein L1. Since VLPs are merely protein and do not contain viral genome, these are considered non-infectious and non-oncogenic, and thus are safer than HPV-attenuated vaccines. VLPs can be produced in bacteria, yeast, or insect cells. Cervarix comprises HPV16 and 18 VLPs, monophosphoryl lipid A (MPL), and aluminum hydroxide (together called adjuvant system 04, AS04) as an adjuvant. MPL is a toll/like receptor 4 (TLR4) agonist that can induce high levels of antibodies as compared to Gardasil and Gardasil 9, both of which contain only aluminum hydroxide as an adjuvant and are produced in Saccharomyces cerevisiae yeast. Gardasil contains VLPs against HPV6, 11, 16, and 18, while Gardasil 9 contains VLPs against HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 [18].

The HPV vaccines currently being produced are based on L1-VLPs, which only provide type restricted immunity, neglecting many other oncogenic HPV genotypes. Consequently, the second generation VLPs, such as L2-VLP and Chimeric L1-L2 VLP, are drawing a lot of attention for their broader genotype coverage. In comparison to L1-VLP, the minor capsid protein, L2, contains type-common epitopes that can provide broad cross-neutralizing antibody responses. Notably, Cervarix can confer a degree of cross-protection against some phylogenetically related types of HPV16 and 18 from the same phylogenetic cluster alpha-9 (HPV16-like: HPV31, 33, 35, 52, 58) and alpha-7 (HPV18-like: HPV39, 45, 59, 68) species groups, owing to its unique adjuvant systems [18].

Adverse Effect

Studies indicate that the most common adverse effect is injection-related local reaction, such as pain, swelling and erythema. Regarding systemic symptoms 50-60% were reported (fever, nausea, vomiting, dizziness, myalgia and diarrhea). Severe adverse effect, such as severe headache 100% of included patients with hypertension, gastroenteritis 76% and bronchospasm with dyspnoea 66%. Both HPV vaccines are classified as Pregnancy Category B by the FDA. Therefore, the vaccine is not recommended for pregnant women, because there are not enough data to ensure safety to the fetus [20, 21].

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