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UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

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Non Melanoma Skin Cancer

GRADUATE THESIS

Zagreb, 2016.

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Abstract

Non melanoma skin cancer is the most frequently occurring human malignancy. It is encountered all over the world, particularly in areas with high exposure to its primary risk factor, sunlight. The pathogenesis involves signature UV mutations in genes coding for tumor suppression and growth signalling. Early identification of suspicious lesions is significant because the various therapies available are most effective for localized disease. The elucidation of the MAPK and PI3K growth pathways in cutaneous squamous cell carcinoma and the Sonic Hedgehog signalling pathway in basal cell carcinoma have led to the development of novel treatments for metastatic disease.

Key words: Basal cell carcinoma, non melanoma skin cancer, cutaneous squamous cell carcinoma

Abbreviations

5-FU: 5-Fluorouracil

AK: Actinic Keratosis

ALA: 5-Aminolevulinic Acid

ATP: Adenosine Triphosphate

BCC: Basal Cell Carcinoma

BD: Bowen's Disease

CDK: Cyclin Dependent Kinase

cSCC: cutaneous Squamous Cell Carcinoma

DNA: Deoxyribonucleic Acid

dsDNA: double stranded Deoxyribonucleic Acid

ED&C: Electrodessication and Curettage

EGFR: Epidermal Growth Factor Receptor

EMT: Epithelial-mesenchymal Transition

FDA: Food and Drug Administration

GLI: Glioma-associated Oncogene Homolog Zinc Finger Transcription Factor

GTP: Guanosine Triphosphate

HER: Human Epithelial Growth Factor Receptor

HPV: Human Papillomavirus

IL: Interleukin

IFNs: Interferons

ITZ: Itraconazole

mAb: monoclonal Antibody

MAL: Methyl 5-Aminolevulinate

MAPK: Mitogen Activated Protein Kinase

miRNA: micro Ribonucleic Acid

MHC: Major Histocompatibility Complex

NK: Natural Killer

NMSC: Non Melanoma Skin Cancer

PCR: Polymerase Chain Reaction

PDL: Pulsed Dye Laser

PDT: Photodynamic Therapy

PI3K: Phosophoinositide 3-Kinase

PKA: Phosphokinase A

PKC: Phosphokinase C

PTCH: Patched

ROS: Reactive Oxygen Species

SMO: Smoothened

SHH: Sonic Hedgehog

SPF: Sun Protection Factor

SUFU: Supressor of Fused

TGF-β: Transforming Growth Factor Beta

TNF-α: Tumor Necrosis Factor Alpha

UVR: Ultraviolet Radiation

UVA: Ultraviolet A

UVB: Ultraviolet B

UVC: Ultraviolet C

XRT: Superficial X-ray Therapy

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1. Introduction

Non melanoma skin cancer (NMSC) is comprised of two major entities: cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC). These malignancies extremely common and the most important risk factor, sunlight, is nearly unavoidable. Cutaneous SCC and BCC do not metastasize often, but can cause significant local destruction along with disfigurement. A variety of therapeutic modalities exist for the treatment of NMSC, but some have limited efficacy in comparison to surgery. Nonetheless, they can be useful in certain situations and often cosmetically superior to surgical treatment. If treated promptly, NMSCs typically have an excellent prognosis.

2. Epidemiology of non melanoma skin cancer

NMSCs are the most frequent malignant tumors amongst Caucasians. Unfortunately, most cancer registries in the U.S. do not collect data on NMSC incidence. Thus, NMSC incidence data is only an estimate. The U.S. crude prevalence of NMSC seems to be approximately 450 cases per 100,000 individuals.[1] In 2010, more than two million cases of NMSC were diagnosed in the United States; a figure exceeding all other cancers combined.[2] Since the 1970s, the estimated incidence of NMSC has been on the rise, probably attributable to an increase in sun exposure and the use of artificial tanning. Caucasian males have a 9-14% lifetime risk of developing cSCC,[1] and Caucasians in general have about a 30% lifetime risk of developing BCC. Australia has the world's highest BCC rate.[3]

3. Risk factors for non melanoma skin cancer

The chance for developing any type of skin cancer is believed to be increased due to exposure to several factors. Sunlight is the most recognized environmental carcinogen for NMSC. Cutaneous SCC is strongly connected to cumulative sunlight exposure, but the relationship between BCC and sunlight seems to be more complex.[4] Older age and male sex are other major risk factors.[5] Relevant phenotypic factors include pale skin that does not tan easily, red or blonde hair, blue eyes, older age, a large number of moles, and a large number of freckles.[6] A personal history of previous NMSC also increases the risk of developing new NMSC.[1]

3.1. Genetic risk factors

Having two or more close relatives who have had NMSC increases the chance of developing the condition,[6] but certain genetic syndromes greatly predispose affected individuals to NMSC development. A mutation on the *PTCH* tumor suppressor gene leads to the development of nevoid basal cell carcinoma syndrome (Gorlin syndrome). These patients may develop hundreds of BCCs and exhibit other physical characteristics such as a broad nasal root, frontal bossing, borderline intelligence, jaw cysts, palmar pits and multiple skeletal abnormalities. Albinism, xeroderma pigmentosum, Bazex-Dupre-Christol syndrome (follicular atrophoderma and BCC) and Rombo syndrome also predispose to the development of BCC.[7] BCC may also occur as a common although less specific finding in other genodermatoses such as Bloom, Werner, Muir-Torre, Cowden syndrome, oculocutaneous albinism and some epidermal nevus syndromes.[3]

3.2. Non genetic risk factors

There are many environmental factors that contribute to the development of NMSC. These factors include ultraviolet radiation (UVR), ionizing radiation, exposure to arsenic, infection with human papilloma virus (HPV), and tobacco use. Development of malignancy is not limited to these factors

and can also occur in chronic inflammatory and immunosuppressive states. The environmental factors are not absolutely avoidable; though, it is important to stress that exposure can be limited.

3.2.1. Ultraviolet Radiation

Sunlight is the main source of UV light/radiation. It contains three types: ultraviolet A (UVA), ultraviolet B (UVB), and ultraviolet C (UVC). The earth's atmosphere filters out UVC, but UVA and UVB cause damage to the skin over time, increasing the likelihood of skin cancer development.[6] UVA is thought to cause DNA mutations by the formation of reactive oxygen species (ROS). Radiation from the UVB spectrum (290-320 nm) is the most important causal factor for development of BCC, and chronic UVR is the main environmental risk factor for development of cSCC. Keratinocyte exposure to UVR can result in the formation of two mutagenic photoproducts: cyclobutane-pyrimidine dimers and 6,4 pyrimidine-pyrimidine dimers. The 'UV signature mutations' C → T and/or CC→ TT may arise from these DNA lesions and are frequently found in NMSCs. ROS may also damage DNA.[7]

Prolonged and high intensity exposure to UVR highly influences skin cancer pathogenesis. Protection from UVR includes wearing sunscreen which is at least SPF30 and staying out of the sun between the hours of 10 a.m. to 4 p.m, the period of most intense UV output. In addition, one can wear photoprotective clothing, sunglasses, and seek shade to minimize exposure.[1] The use of indoor tanning is associated with a significantly increased risk of NMSC, especially if used before age 25.[5]

3.2.2. Ionizing radiation

Radiation exposure leads to inflammatory processes and alters cellular proliferation due to transcriptionally activated pro-inflammatory cytokines and growth factors. Ionizing radiation leads to the development of often multiple and recurrent BCCs on the sites thus exposed.[8]

3.2.3. Arsenic

Exposure to arsenic is an environmental risk factor increasing the probability of NMSC development.

Arsenic is a metalloid found in the earth's crust, and humans are typically exposed to it in groundwater or occupationally. Those who produce pesticides, herbicides, wood preservatives, animal feed additives, semiconductors and transistors, glass, and pigment, have an increased risk of exposure. Normal human epidermal keratinocytes exposed to toxic concentrations of arsenic undergo changes in gene expression associated with skin carcinogenesis (ie. oxidative stress). Dermal manifestations of these lesions include hyperpigmentation as well as hyperkeratosis.[9]

3.2.4. Human papillomavirus

"The human papillomaviruses (HPVs) consist of a heterogeneous group of capsid-enclosed dsDNA viruses from the *Papillomaviridae* family that display a distinct tropism for mucosal or cutaneous squamous epithelia."[10] The more than 170 HPV types have been categorized in genera on the basis of the homologous nucleotide sequence of the major capsid protein L1. The beta genus, a large group of cutaneous HPV types, is suspected to be involved with the development of NMSC. The oncogenic potential of the beta-HPV genus came to light after isolation of the virus from the skin of patients with the rare genetic disorder Epidermodysplasia verruciformis. These patients have a high susceptibility to HPV infection due to an impaired immune system. Thus, they develop extensive verrucosis consisting of confluent flat warts which often evolve into multifocal cSCCs in sun-exposed areas. Similarly, beta-HPV types have been isolated from the skin of immunosuppressed organ transplant recipients, another group with an extremely high risk of developing NMSC. The skin of healthy individuals is also frequently infected with beta-HPV types, but the role of HPV in development of NMSC in the general population is not entirely clear. Quantitative PCR of beta-HPV viral load demonstrates that only a minority of skin cancer cells contain viral DNA. Perhaps the beta-HPV types initiate carcinogenesis but are not required during the later stages for neoplastic phenotype maintenance. Beta-HPV likely facilitates the accumulation of UV-induced DNA mutations, but is not needed for cancer maintenance.[10]

3.2.5. Tobacco use

Cigarette smoking suppresses immune responses and decreases cutaneous blood flow, mechanisms which may increase skin cancer risk. Ever smokers had a higher risk of cSCC and have a slightly higher risk of BCC. Smoking causes downregulation of gene expression in the *Notch* pathway, which normally inhibits growth in cSCC and BCC.[11]

3.3. Other risk factors

A few other risk factors deserve mention. Chronic dermatoses and scars predispose to development of cSCC. For example, Marjolin's ulcers are cSCCs that develop in areas of chronic scarring. Exposure to x-rays, polycyclic hydrocarbons, and insecticides can also predispose to cSCC development. BCC may develop with a nevus sebaceous, a flesh-colored to yellow plaque on the scalp present at birth. *p53* gene mutations are another risk factor for BCC.[1]

3.4. Chronic inflammation

In chronic inflammation, the long-term production and consequent accumulation of cytokines and chemokines induces a locally immunosuppressive environment that may lead to tumor development. A number of similarities exist between chronic inflammation and tumorigenesis. Certain intracellular pathways, namely *Ras*, *Hedgehog*, and WNT, are deregulated in both tumorigenesis and in the chronic inflammation of a non healing wound. The epithelial-mesenchymal transition (EMT) occurs in both processes. Through EMT, the epithelial cells lose their polarity and cell-cell adhesion to gain migratory and invasive characteristics, becoming mesenchymal stem cells. The fibrosis of wound healing creates a microenvironment featuring many growth factors, cytokines and chemokines also found in tumors.[12]

3.5. Immunosuppression

In solid organ transplant recipients, skin cancer, specifically cSCC, is the most frequently reported post-transplant malignancy.[7] In comparison to the general population, there exists an inverse ratio of cSCC to BCC. BCCs are typically the most frequent NMSC in the general population, but in organ transplant recipients, cSCC becomes the most common NMSC. Organ transplant recipients tend to develop NSMC at a relatively young age, multiple lesions and tumors with an increased metastatic potential. Unlike the prognostically favorable NMSCs occurring in the general population, lesions developing in organ transplant recipients are concerning due to their higher incidence, multiple tumors, and aggressive behavior.[13]

4. Pathogenesis of non melanoma skin cancer

The transformation of a keratinocyte leads to the development of NMSC. Cutaneous SCC originates from the top layer of the skin, whereas BCC evolves from the skin's basal layer.[11] Disease progression may involve a variety of causal suspects including familial inheritance patterns, exposure to certain environmental carcinogens and immunosuppressive states. Cutaneous SCC arises from the precursor lesion of actinic keratosis (AK) while sporadic BCC develops de novo.[7]

4.1. Cutaneous squamous cell carcinoma

Cutaneous SCCs often possess activating mutations in the *RAS* gene family (*H-RAS*, *K-RAS*, *N-RAS*, and *R-RAS*) which encode GTPases that activate when stimulated by receptor tyrosine kinases, G-protein-coupled receptors, or integrins. RAS proteins signal to serine/threonine kinases of the RAF family, thus initiating the MAP kinase signalling cascade which ultimately leads to activation of transcription factors leading to cell cycle progression, cell proliferation, and cell survival. The *H-RAS* gene was found to be the most frequently mutated *RAS* family gene in cSCC. Mutations of *RAS* are not sufficient for the development of malignancy. Chromosomal deletions are also common in cSCCs, especially of *9p*, the region encoding the tumor suppressor *CDKN2A*. Furthermore, the *TP53* gene, which encodes, the tumor suppressor protein p53, often contains the UV signature CC → TT or C → T tandem transition mutations. Overexpression of miRNA-205 found in some cSCC may also be tumor promoting.[1]

4.1.1. Actinic keratosis

AK or solar keratosis is induced primarily by UVR and develops in photoexposed skin areas of the elderly. The most common event seems to be UVR induced mutations in the *p53* tumor suppressor gene.[7] AKs also sometimes harbor *H-RAS* mutations and deletions in the *CDKN2A* locus, findings consistent in a precursor lesion to cSCC.[1] These suspicious skin changes present as ill-defined to skin-

colored hyperkeratotic papules found on skin chronically exposed to the sun. Kalokasidis *et al.* describe the histopathological features of AK to include "hyperkeratosis and/or ulceration; columns of parakeratosis, atypical keratinocytes, separated by areas of orthokeratosis; basal atypical keratinocytes with varying degrees of overlying loss of maturation, hyperchromatism, pleomorphism, increased and abnormal mitoses, dyskeratosis; variable superficial perivascular or lichenoid chronic inflammatory infiltrate; solar elastosis, (and) lack of dermal invasion."[7]

4.1.2. Bowen's disease

Cutaneous SCC in situ, or Bowen's Disease (BD), typically presents as a well demarcated and slowly enlarging erythematous patch or plaque with a scaling or crusted surface. It typically occurs on poorly healing body sites on the lower limbs and head and neck of elderly patients. BD has a 3-5% risk of progressing into invasive cSCC.[14]

4.2. Basal cell carcinoma

The cell surface receptor Patched 1, the protein product of *PTCH*, inhibits Smoothened (SMO), a G-protein-coupled receptor. A mutation in *PTCH* may cause cessation of SMO inhibition by Patched1, thus initiating a signal cascade which leads to activation of transcription factor GLI1. The loss of PTCH protein or uncontrolled expression of SMO results in dysregulation of the pathway and cell proliferation and differentiation. Seventy percent of sporadic human BCCs contain mutations which lead to defects of either the PTCH or SMO proteins.[1]

5. Diagnosis and assessment of non melanoma skin cancer

Early diagnosis offers the best prognosis for NMSC. Biopsy and histopathologic workup confirms the diagnosis, and evaluation of spread helps determine the proper choice of therapy. Identification of high-risk factors further narrows the most appropriate therapeutic choices.

5.1. Clinical presentation and workup

NMSC commonly develops on sun-exposed skin, particularly of the head and neck. Cutaneous SCC may appear as a rough or scaly area or red bump. BCC varies in its appearance, but it frequently looks like a smooth, pearly, or waxy raised bump. It may also appear to be a firm, flat scar. A sore that does not heal, a new growth, or a change in an old growth may all herald skin cancer. These suspicious lesions warrant a complete skin examination. The physician also collects information regarding patient sun exposure and other medical history and examines the lymph nodes.[15] A small lesion is defined as measuring less than 2 cm.[16]

5.2. Biopsy

A lesion suspicious for cancer identified during the complete skin examination must undergo a biopsy. The physician may choose to perform either a shave, punch, or excisional biopsy. In a shave biopsy, a small portion of the abnormal area is shaved off with a razor, and a punch biopsy involves removing a circle of tissue with a special instrument. The entire abnormal area is removed in an excisional biopsy.[15] Punch and shave biopsies have a similar diagnostic accuracy, but for most patients, a shave biopsy incorporating the full depth of the lesion is the preferred method. An excisional biopsy further serves as definitive therapy in a patient with an obvious BCC and for whom cosmetic outcome is not a priority.[17]

5.3. Histopathology

All BCCs contain "aggregations of basaloid keratinocytes that are surrounded by stromal tissue and typically demonstrate a connection to the epidermis. Basaloid cells resemble the basal keratinocytes of normal epidermis and are characterized by intensely basophilic, large, relatively uniform nuclei, and scant cytoplasm."[17] BCCs can be classified according to their histopathologic features: indolent-growth and aggressive-growth. Nodular and superficial BCCs are indolent-growth subtypes, and morpheaform, infiltrative, micronodular, and basosquamous BCCs are aggressive-growth subtypes. The aggressive-growth subtypes tend to cause extensive local destruction and have a higher recurrence rate. A single specimen displaying combinations of these histopathologic patterns is referred to as a mixed histology tumor. Forty percent of primary BCCs are mixed histology tumors.[17]

5.3.1. Cutaneous squamous cell carcinoma variants

Cutaneous SCC may present as a particular morphology. Lower lip SCC begins as scaly leukoplakia or actinic cheilitis and eventually progresses to a tumor nodule. Genital SCC is frequently associated with lichen sclerosus and atrophicans. Erythroplasia of Queyrat is a precursor of penile SCC. Keratoacanthoma is considered a cSCC clinical subtype. Cutaneous cSCC can also develop on scar tissue.[7]

5.3.2. Basal cell carcinoma variants

The clinical subtype of BCC will further determine the encountered clinical features. Nodular BCC is the most common subtype, and it typically occurs on the head and neck as a well-defined, firm translucent or pearly papule or nodule, with a peripheral rolled border and telangiectasias. Pigmented BCC is a subtype of the nodular BCC, and it appears as a translucent, hyperpigmented nodule. Ulcerated BCC, also known as ulcus rodens, displays central necrosis. The morpheaform or sclerosing BCC is clinically distinguished by its ivory-white appearance. It is also more likely to metastasize.

Fibroepithelioma of Pinkus presents on the lower back as a pink papule.[7] Superficial BCC is less than 2 mm deep in relation to the skin surface.[16]

5.4. Recurrent carcinoma

Because NMSC metastasis is rare, the prognosis is generally very good unless the cancer harbors certain characteristics linked to an increased risk of cancer recurrence or metastasis.[15] Risk is assessed by identification of parameters indicating high-risk behavior. Possession of any one parameter places the tumor in the high-risk category. Clinical factors of high risk are "tumor location and size, the status of tumor borders (well-defined versus ill-defined), whether the tumor is primary or recurrent, certain settings of immunosuppression, and tumors developing in previously irradiated sites."[4] NMSCs developing in the head and neck are more likely to recur than NMSCs developing on the trunk and extremities. Tumors greater than 2 cm in diameter also have an increased risk of recurrence. Perineural involvement occurs more frequently in cSCC than BCC, and it greatly increases the risk of recurrence. Patients with well-differentiated tumors have a better prognosis than patients with poorly differentiated neoplasms. Cancers displaying an aggressive growth pattern also have a higher risk of recurrence. Cutaneous SCC has a few additional clinical high-risk factors which include a tumor developing on the site of a chronic inflammatory process such as chronic scarring, a rapidly growing tumor, and a tumor causing neurological symptoms. Histologically, the presence of desmoplasia in cSCC also increases the risk of recurrence and metastasis.[4]

6. Treatment of non melanoma skin cancer

"The goal of treatment of BCC is to completely remove the tumor and maximally preserve function and cosmesis at the site of treatment."[17] The presence or absence of aggressive histopathological and clinical features further determines the specific therapeutic option. The location of the lesion forms the other important consideration in treatment choice, as cosmesis and preservation of function are key in certain areas, such as the face. Patient preference also plays a role in treatment selection.[17]

Surgical excision and electrodesiccation and curettage (ED&C) are most frequently used for BCCs at low risk for recurrence. Mohs surgery has the highest cure rate, and is the treatment of choice for lesions at increased risk of recurrence and where anatomic relations and functionality demand maximal preservation of surrounding tissue.[17] Radiation therapy may be an appropriate choice for older, debilitated patients not able to tolerate extensive surgery.[15] Cryosurgery, pulsed dye laser therapy (PDL), topical 5-fluorouracil (5-FU) or imiquimod, and photodynamic therapy (PDT) are less frequently used treatments and typically only for low-risk lesions.[17]

The physician determines the cancer stage to select the most appropriate treatment. Stage 0 represents malignant involvement of only the top layer of the skin, also called carcinoma in situ. In stage I, the cancer is 2 cm in diameter or smaller, and in stage II, the cancer is larger than 2 cm in diameter. Stage III represents local invasion of the cancer below the skin to cartilage, muscle, bone, or nearby lymph nodes, and Stage IV cancer has spread to distant parts of the body.[15]

6.1. Surgical treatment

Surgical treatment is the primary option with regard to therapy choice for NMSC. The main benefit of such treatment is the potential to fully cure the patient from the disease. A significant proportion of patients will require surgery, and the decision on the type of surgical procedure should be made based on tumor characteristics and clinical signs. Factors to consider include the type of NMSC, size of the

tumor, whether the cancer is primary or recurrent, stage of the cancer and location of the tumor.[15]

6.1.1. Surgical excision

Surgical excision is a frequently used treatment option after diagnosis of NMSC. Both cSCC and BCC are excised with a margin of healthy skin which is sent to the pathologist for examination to ensure complete tumor removal. Since cSCC is more invasive, it is excised with a larger margin of normal tissue; 4-6 mm for-low risk cSCC and 6-10 mm for high-risk cSCC.[18] The mainstay of treatment for a small (less than 2 cm) BCC on low-risk sites (trunk/extremity) without aggressive histologic features is standard excision with 4 mm margins.[16]

6.1.2. Electrodessication and curettage

ED&C is a surgical technique that combines superficial ablation with surgical scraping of the affected skin with a curette. The lesion should first be electrofulgurated, and then the devitalized epidermis is curetted. This process may be repeated once. If the lesion requires further ED&C, it should be excised. Development of a hypopigmented scar is the the main side effect of this treatment. Low-risk superficial and nodular primary BCCs on the extremities and trunk are most amenable to treatment with ED&C. For appropriately selected lesions, ED&C has achieved a cure rate of 95.1% in one large prospective cohort study. ED&C should not be used to treat lesions displaying aggressive features on histology because of high recurrence rates.[17]

6.1.3. Mohs micrographic surgery

Mohs micrographic surgery is a common therapeutic choice in the treatment of NMSC. This very specialized surgical procedure ranks the highest in terms of cure rate among all surgical treatments. It is based upon a technique which removes the skin cancer and surrounding tissue in series of layers until the remaining healthy tissue shows no sign of malignancy under a microscope. This use of in-office pathohistological scrutiny allows the maximum amount of healthy tissue to be conserved and provides

aesthetically pleasing results. The indications for Mohs micrographic surgery include anatomic location, histologic and gross characteristics of the tumor, and its pattern of recurrence. A study done by Dim-Jamora and Perone states the need for tissue conservation in cosmetically challenging locations (such as periocular, perioral and auricular region tumors) as an indication for Mohs micrographic surgery. Tumors present in functionally sensitive areas (such as acral regions of the hand and digits or nail units) and areas of high recurrence should also be considered for this type of therapy. Cutaneous tumors that display an asymmetric and irregular conformation and BCC of certain histological subtypes are indicated for the Mohs procedure. In addition, primary BCC and cSCC with indistinct borders can be treated, especially if the tumor is on actinically damaged skin. The indications for Mohs micrographic surgery are quite diverse and may be based on either pathology or clinical assessment.[19]

6.1.4. Pulsed dye laser therapy

BCC can also be treated with PDL, especially if a cosmetically appropriate result is desired. PDL is currently being used to treat vascular skin lesions (e.g., port-wine stains, hemangiomas, and telangiectasias), including the highly vascular BCCs. It is hypothesized that PDL destroys the BCC's blood supply, leading to death of the tumor. The benefits of PDL over conventional surgical therapies include its time efficiency, simplicity, short recovery time and the smaller risk of side effects commonly associated with surgical therapies. The disadvantages of PDL include lack of universal access to laser therapy, requirement of several in-office treatments, and the lower response rate when compared to more traditional therapies.[20]

6.1.5. Cryosurgery

The basis of cryosurgery is the use of liquid nitrogen at -196 Cº to induce subzero temperatures which result in cell death. The frozen tissue sloughs off and subsequently heals. To destroy malignant lesions, the procedure utilizes at least two freeze-thaw cycles with a tissue temperature of -50 Cº and a duration of freezing of 40 to 60 seconds. To ensure eradication of subclinical extension, a margin of clinically

normal tissue is also destroyed. The disadvantage of this treatment is that there is no histologic confirmation of complete tumor removal. After the proceduere, a scar-like area may develop, and the clinician may have difficulty evaluating the site for future recurrence. Treatment of primary BCC does result in a 5-year recurrence rate ranging from 4% to 17%.[16]

6.2. Radiation therapy

Indications for radiation therapy include patient ineligibility for surgery due to other medical problems or an inoperable tumor due to its size or location. Radiation therapy may also be of use if the patient refuses surgery or in an incomplete surgical excision.[21] It involves several weeks of intensive treatment, and tumor margins are not histologically confirmed.[18] The probability of tumor recurrence depends on the size of the tumor. Five-year control rates of 96.1% (T1), 95.6% (T2) and 88.6% (T3) have been determined from a large retrospective series.[21] Some patients may not tolerate the side effects which include malaise, nausea, erythema, telangiectasia, hypopigmentation, epidermal atrophy, and soft-tissue necrosis.[18] The use of radiation therapy in young patients may eventually give rise to a secondary malignancy.[1]

6.2.1. Superficial x-ray radiation

Superficial x-ray therapy (XRT) utilizes x-ray photons generated from electrons interacting with a heavy metal target. The electrons are generated by an electrically excited filament and accelerated across an electric potential. XRT has a limited depth of penetration into tissue because of rapid attenuation with atoms in the tissues traversed. Most NMSCs lie within a few millimeters of the skin surface, and XRT is sufficient for treatment of such neoplasms.[1]

6.2.2. Electron beam radiation

Deeply penetrating electrons are more effective therapy for tumors more than 5 mm thick. Electron beam radiation is produced by linear accelerators capable of delivering electrons at several different

energies, thus allowing for selection of penetration depth. The megavoltage electrons produced from electron beam radiation are more difficult to shield than the kilovolt electrons produced by XRT.[1]

6.2.3. Brachytherapy

Brachytherapy involves the placement of a radioactive source onto or into the body. This local treatment is most effective for small (less than 2 cm wide) primary and superficial (less than 2 mm deep) BCCs. It generates superb functional and cosmetic results. The efficacy of interstitial brachytherapy efficacy has to be more thoroughly studied, but a 4-year recurrence rate of 0.7% for the surgery and 7.5% for the brachytherapy group has been reported as the result of a randomized controlled trial involving primary facial BCCs.[16]

6.2.4. Adjuvant radiation therapy

Adjuvant radiation therapy is administered to areas with an increased possibility of residual disease. Postoperatively, it is typically indicated for NMSC involvement of the bones and nerves, perineural invasion, multiple recurrences of carcinoma, and for positive tumor margins. However, more research is needed to determine exactly which patients benefit from adjuvant radiation.[18]

6.3. Topical chemotherapy

Topical treatments hold a range of benefits which make them appealing therapies for destroying precancerous lesions and superficial tumors. Usage of topical medications decreases the risk of adverse side effects associated with the metabolism of systemic therapy. As these agents are locally acting, it is unlikely that a systemic allergic reaction will occur. The drugs are applied to the skin as creams and the doses and dosing schedule will vary from patient to patient. The possibility of treating wider areas and scar free healing are advantages of topical chemotherapy. Disadvantages include the sometimes severe inflammatory and erosive reactions, necessity for patient compliance, limited depth

of action and lack of histological control.[20]

6.3.1. Imiquimod

Imiquimod is a synthetic amine that belongs to the imidazoquinoline drug family. When applied topically, it can have significant immune response modifier activity. This drug has both antitumor and antiviral effects. Many studies have shown imiquimod to have direct and indirect actions on the immune system making it effective in the treatment of NMSC. Imiquimod directly induces cell death through the intrinsic apoptotic pathway by upregulating proapoptotic proteins of the Bcl-2 family, specifically Bax and Bak. The increased expression of these proteins provides a direct cellular mechanism by which cutaneous malignancy can be treated. Indirect effects also contribute to imiquimod's activity through release of cytokines (IL-12, TNF-α, IFN-γ) which act to stimulate a cell-mediated immune response thus providing indirect antitumor activity. These cytokines increase levels of cytotoxic T cells and natural killer (NK) cells in the area of application to block angiogenesis and interfere with tumor growth.[21]

6.3.2. 5-Fluorouracil

The pyrimidine analog and antimetabolite, 5-fluorouracil (5-FU), is a topical treatment for AKs and superficial BCCs.[16] As a 5% prescription cream, the cytostatic 5-FU is applied twice daily for 3-12 weeks until erosions develop. In the treatment of superficial BCC, topical 5-FU achieved the average cure rate of 80%, making it slightly inferior to the 83% cure rate achieved with imiquimod. Both imiquimod and 5-FU are superior to methyl aminolevulinate's (MAL) cure rate of 73% in PDT.[20]

6.4. Immunotherapy

Immunotherapy is a form of biological therapy that uses various substances to stimulate or suppress the immune system to assist the body in fighting cancer, infection and other diseases. Cytokines, vaccines,

and some monoclonal antibodies (mAbs) are all types of immunotherapy.[22]

6.4.1. Interferons

IFNs are naturally occurring glycoproteins possessing antiproliferative, antiviral and immunomodulatory qualities. Leukocyte (α), fibroblast (β) and immune (γ) IFNs are the three antigenically distinct forms produced by human cells. IFNs induce antiproliferative effects by inhibiting mitosis and growth factors, downregulating *c-myc*, *c-fos* and *c-ras* oncogenes, activating proapoptotic genes and proteins, repressing antiapoptotic genes, modulating differentiation and promoting antiangiogenic activity. Furthermore, IFNs upregulate the immune system by inducing expression of class I and/or II major histocompatibility complex (MHC) antigens on both immunocompetent and tumor cells. Finally, IFNs increase the activity and number of NK cells, macrophages, and dendritic cells. Full-thickness excision and cryosurgery are still more successful BCC treatments with 95% and 94-99% cure rates, respectively. Influenza-like symptoms are the principal adverse events occurring with IFN therapy.[1]

6.5. Photodynamic therapy

PDT is a relatively recent development in the management of NMSC. A photosensitizing drug is topically applied to the lesion and then is subsequently activated by a particular wavelength of light to produce ROS. The commonly used photosensitizers, 5-aminolevulinic acid (ALA) and its esterified derivative methyl 5-aminolevulinate (MAL), are precursors of the endogenous photosensitizer protoporphyrin IX.[23] After the photosensitizer is exposed to specific wavelengths of light, it leaves the ground state to enter an excited singlet state. Intersystem crossing ensues, and the photosensitizer enters a longer-lived excited triplet state through which it can transfer a hydrogen or electron to the surrounding molecules to produce free radicals or transfer energy to oxygen, producing singlet oxygen. In biological systems, the O_2 species is highly active and can only diffuse a short distance before deactivation during its miniscule lifetime. In this manner, the O_2 mediated damage occurs locally. Thus,

there is limited destruction of healthy tissue, and a superior cosmetic result is achieved.[23]

The topical photosensitizers ALA/MAL are now available in most dermatologic clinics for the treatment of AK, superficial BCC, and cSCC in situ (BD). The cosmetic outcome of PDT is superior to standard therapy, but it should be chosen with care as a treatment modality. For example, topical MAL-PDT is effective in nodular BCC, although with lower efficacy than excision surgery. It could be considered when surgery may be suboptimal. Furthermore, even though PDT has been proven effective in the treatment of BD, it should not be used alone for cSCC lesions with potential for regional spread. As a local treatment, PDT is limited in its ability to treat deep-set disease.[23]

6.6. Treatment of advanced cutaneous squamous cell carcinoma

Cutaneous SCC has a much greater propensity than BCC to involve regional lymph nodes. Palpable lymph nodes discovered on physical examination call for either a fine needle aspiration or open biopsy. If the findings are positive, regional lymph node dissection following the corresponding pathway is the treatment of choice. When surgery is not possible, irradiation of the lymph nodes is the alternative therapeutic option.[4]

6.6.1. EGFR pathway targeted therapy

The epidermal growth factor receptor (EGFR) belongs to a family of transmembrane protein kinase receptors comprised of: EGFR (HER1 or ErbB1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). These receptors are activated by several different ligands, ultimately causing signalling through the parallel MAPK and PI3K pathways leading to cell growth, angiogenesis, migration and invasion. Agents targeting EGFR are mAbs directed at the receptor's extracellular domain.[24]

6.6.1.1. Cetuximab

The recombinant human/mouse chimeric mAb cetuximab targets EGFR and inhibits the binding of epidermal growth factor through competitive inhibition. Thus, downstream phosphorylation and activation of receptor-associated kinases is blocked, causing inhibition of cell growth and resulting in apoptosis. Cetuximab also acts through classical immunologic mechanisms; it mediates complement- and cell-dependent lysis of cells expressing tumor antigens.[25]

6.6.2. Systemic chemotherapy

Locally advanced or metastatic cSCC requires the use of chemotherapy. Methotrexate, bleomycin, doxorubicin, and cisplatin, alone or in combination with 5-FU, have been used.[18]

6.7. Treatment of advanced basal cell carcinoma

Typically, BCC lesions grow slowly; however, in some cases, they can become extremely aggressive and invade local tissue. Local destruction and disfigurement may ensue if the tumor penetrates into underlying structures, such as the eyelid or internal canthus in BCC of the head and neck region.[3] BCC has an extremely low metastatic rate of < 0.1%, but as the tumor continues to grow, the metastatic rate will also increase proportionately. The risk of metastasis can go up to 50% in lesions which are greater than 10 cm in diameter. Metastasis most commonly involves the regional lymph nodes and lungs, but metastases to bone and bone marrow have also been reported.[2]

6.7.1. Sonic Hedgehog pathway targeted therapy

The Sonic Hedgehog (SHH) signalling pathway is a key regulator of cell proliferation, cell differentiation and tissue polarity. It is felt that this pathway plays a major role in the maintenance of the relatively chemo- and radio-resistant subset of cancer stem cells. The SHH protein, an oncogenic

ligand, binds and inactivates the transmembrane protein PTCH1, which normally inhibits the activity of the transmembrane protein Smoothened (SMO).[27] Physiologically, the SHH protein is absent, and the suppressor protein PTCH1 forms a complex with SMO, keeping the SHH signalling pathway inactive.[3] Thus, SHH ligand binding, through the inactivation of PTCH1, leads to SMO mediated release of a glioma-associated oncogene homolog zinc finger transcription factor 1 (GLI1) from it cytoplasmic sequestration by Suppressor of Fused (SUFU). GLI1 translocates to the nucleus and directs the transcription of genes relevant to cell proliferation, apoptosis suppression, and stem cell self-renewal. Additionally, GLI transcription factors are upregulated by TGF-β, PI3K-AKT, PKC-α, and k-RAS in particular. Furthermore, GLI proteins are downregulated by p53, PKA, and PKC-δ.[27] In BCC, the SHH signalling pathway becomes active due to mutations in PTCH, found in 90% of sporadic BCCs, and SMO mutations, found in 10% of BCCs.[3]

6.7.1.1. Vismodegib

The oral small-molecule agent, Vismodegib, is a first-in-class SMO inhibitor for the treatment of both locally advanced and metastatic BCCs.[28] It was approved by the FDA in 2012 after the positive results of the ERIVANCE BCC study. This research documented a 30% partial response rate in patients with metastatic cancer. Patients with locally advanced BCC achieved an overall response rate of 43% and a partial response rate of 21%. The median duration of the response lasted 7.6 months, while the median progression free survival lasted 9.5 months. Thirty percent of patients experienced adverse events which included muscle spasms, dysgeusia, weight loss, alopecia, and fatigue.[3]

6.7.1.2. Sonidegib

The new SMO inhibitor, Sonidegib, was approved by the FDA in 2015 for the treatment of locally advanced BCCs. It blocks SHH signalling by selectively inhibiting SMO. An objective response rate of 35% was reported in clinical trials examining the effectiveness of sonidegib in patients with advanced BCC. A recent open-label study demonstrated that patients with advanced BCCs who were

previously resistant to treatment with vismodegib were also refractory to treatment with sonidegib. This study suggests that chemoresistance occurs between different SMO inhibitors.[28]

6.7.1.3. Itraconazole

The triazole antifungal agent, itraconazole (ITZ), is widely used for the treatment of dermatological and systemic fungal infections. It disrupts fungal cell membrane integrity by decreasing ergosterol synthesis through inhibition of the lanosterol 14 α-demethylase enzyme. ITZ can be administered intravenously, but it is typically given orally as capsules or solution. Recently, ITZ and its primary metabolite hydroxyitraconazole were identified as inhibitors of the SHH pathway. Furthermore, ITZ seems to be able to reverse resistance to current SHH inhibitors such as vismodegib. A small open label trial involving patients with BCCs demonstrated a reduction in tumor cell proliferation, SHH pathway activity, and tumor area. Besides the inhibition of SHH signalling, the anticancer activity of ITZ may be explained through its antiangiogenic effects, autophagy induction and reversal of multidrug resistance. Because ITZ acts on a different molecular target than vismodegib, combining the two drugs may limit acquisition of drug resistance. Nausea, abdominal pain, and rash are the most common side effects.[29]

6.7.2. Systemic chemotherapy

In the event of the development of the extremely rare metastatic BCC, a variety of chemotherapeutic agents are available. Doxorubicin, 5-FU, cisplatin, cyclophosphamide, vincristine, etoposide, bleomycin, and methotrexate are commonly used drugs, either alone or in combination. A polychemotherapy based on cisplatin appears to be the most active, but it is limited by renal and hematological toxicity.[2]

7. Conclusion

Non melanoma skin cancers are ubiquitous but also preventable and easily treatable malignancies if detected in the early stages. Minimizing exposure to sunlight and application of sunscreen have been the cornerstones of prevention. Ultraviolet radiation has a central role in the development of NMSC, but more remains to be discovered as to the exact pathogenetic mechanism of tumorigenesis. Surgery continues to be the most effective treatment among the currently available therapies. The refinement of other local therapies is important in managing NMSC presenting in cosmetically sensitive regions where surgery would lead to significant disfigurement. Experimentation with combinations of the aforementioned treatments may result in higher cure rates than the cure rates reported with the use of single modalities.

8. References

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