Non-Invasive Strategies for the Treatment of Nonmelanoma Skin Cancers

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ABSTRACT

Introduction: The most common dermatological malady among Caucasians is skin cancer. Cutaneous neoplasms may be classified into two distinct classes: melanoma and nonmelanoma skin cancer (NMSC). The latter consists of two primary histological subcategories, namely basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), both of which are keratinocyte carcinomas. For decades, surgical resection has been the leading course of treatment for both MSC and NMSC malignancies. Nevertheless, the performance of surgery may be impacted by various considerations, including comorbidities of the patient, the anatomical site of the lesion, potential intolerance for repeated tissue excisions to ensure complete elimination of the cancer, and patient care setting. Due to the aggressive metastatic ability and consequent mortality of cutaneous melanoma (CM), there is not much variety in the proposed treatment methods for the care and eradication of this cancer. In its clinical guideline for the treatment of CM, the American Academy of Dermatology (AAD) advocates for surgical excision of the tumor to maximize patient survivability. While surgical removal is a feasible management option for NMSCs as well, the lesser-malignant nature of such lesions may allow for greater leeway in the realm of treatment. Although available treatments of BCC and SCC are generally effective in eradicating cancer, some of their disadvantages include the incomplete resection of the growth, poor postoperative quality of life implications, limited cosmetic results, and costliness. Due to globally escalating rates of NMSC presentation, the development of noninvasive treatment methods is imperative.

Methods: Twenty-five years' worth of published medical literature (1995–2021) was evaluated using PubMed and Google Scholar databases. Both surgical and noninvasive treatment

modalities were examined, with particular emphasis allocated to the collection of data on novel therapies in the care and management of NMSC therapy.

Data: This review will address and delineate current, non-invasive strategies for the treatment of nonmelanoma skin tumors. Additionally, it will introduce emerging noninvasive treatments that may have therapeutic implications in the realm of typically nonfatal cutaneous cancers.

Results and Discussion:

The development of noninvasive therapies has drastically changed the face of skin cancer management. Nonsurgical treatments including imiquimod, 5-fluorouracil, radiation therapy (RT), as well as photodynamic therapy (PDT) have gained greater use in the care and management of NMSC. Moreover, cannabinoids as well as topical formulations derived from phytonutrient-rich plants of the genuses *Armeniaca, Solanum*, and *Rubus* are being increasingly considered for use in the primary and adjuvant treatment of non-fatal cutaneous malignancies. Such advancements have greatly enabled the conduction of further studies in the search for more effective and tissue-salvaging therapies for the treatment of NMSC.

INTRODUCTION

Skin cancer is the most frequent malignant neoplasm among Caucasians, and approximately 20% of Americans will develop some form of cutaneous disease in their lifetime (Robinson, 2005). Cancers of the skin may be classified into two distinct classes: melanoma and nonmelanoma. Nonmelanoma skin cancer (NMSC) consists of two major histological subcategories, namely basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), both of which are keratinocyte carcinomas. Over the past few decades, the global incidence of skin cancer has risen drastically. While NMSC is associated with a lower risk of morbidity and mortality than melanoma, it constitutes the largest proportion of neoplasms diagnosed per annum. These statistics, compounded by its rising incidence rates, have generated much concern among healthcare professionals. Nonmelanoma cancers of the skin have the highest frequency of presentation among all other forms of malignancies combined. According to a 2013 study which analyzed the long-term trends in cutaneous cancers across the U.S., approximately 3.5 million cases of NMSC are diagnosed per annum. This parameter greatly surpasses the 1.63 million diagnoses per year of all other cancers combined (Perera & Sinclair, 2013). Regarding the prognosis of nonmelanoma neoplasms, studies have reported a 5-year survival rate of 95%, and a mortality rate of approximately 1% to 2% (Gloster and Broadland, 1996; Skidmore & Flowers, 1998).

Melanoma

Melanoma skin cancer (MSC) is a malignancy of dermal cells known as melanocytes. Melanocytes, which play a critical function in skin pigmentation through the production of *melanin*, are specialized cells located at the base of the epidermis. Although cutaneous malignant melanoma (CMM) only accounts for approximately 1.7% of all cancer-related deaths and >2%

of all diagnosed tissue lesions, it has the highest morbidity and mortality rate among dermatological maladies, accounting for 60% of all skin-cancer related deaths (Cullen et al., 2019; Schadendorf et al., 2018). Approximately 90% of all MSCs are sporadic, and thereby attributable to environmental factors capable of inducing genetic mutations (Schadendorf et al., 2015). Pre-programmed cellular repair mechanisms are crucial to the reversal of genomic damage occurring in cutaneous cells periodically exposed to intense sunlight. In the event that such internal repair systems cease to function, mutations in melanocytic DNA may promote the rise of tumorigenic growths. Genomic alterations often occur years prior to the development of skin cancers. Genetic analyses of cutaneous melanomas (CMs) have evidenced mutations in the *BRAF* oncogene, as well as the *NRAS, CDKN2A,* and *TP53* genes (Hayward et al., 2017; McDaniel & Badri, 2019). Of the existing subtypes of melanoma, the most prevalent form is known as *superficial spreading melanoma*. This variety of cancer accounts for 70% of reported cases of MSCs. Other forms include *nodular*, *lentigo maligna,* and *acral litigious* melanoma, all of which comprise the lesser common varieties of the cancer. Melanoma primarily develops on acral and cutaneous surfaces of the body including the face, trunk, and superior and inferior limbs. Albeit less common, melanomas are also known to form on mucosae of the oral and genital regions.

Although CMM is not the most prevalent form of skin cancer, its aggressive metastatic ability warrants its classification as the most severe among cutaneous diseases. A 2015 study analyzing relative survivability of European patients diagnosed with CM reported peak mortality rates within 5 years of initial diagnosis. The Breslow evidence-based staging system for CM constitutes a series of clearly defined criteria by which the progression of melanoma may be assessed. Also known as ‘Breslow’s tumor thickness,’ this prognostic factor measures the extent

to which the malignancy has metastasized into subdermal layers of skin. Thinner skin melanoma lesions, for instance, have better prognoses than deeper-penetrating, more advanced ones (Schadendorf et al., 2015). This method of measuring melanoma prognosis has been approved and implemented by the World Health Organization (WHO) Melanoma Program as well as the European Organization for Research and Treatment of Cancer Melanoma Group (Balch et al., 2004). In light of this, early detection and routine medical screening are critical in preempting the advancement of CMM and improving prognosis and treatment response (Gloster & Brodland, 1996). The following diagnostic tool, consisting of three distinct stages, has been proposed for the diagnosis of CM: (1) pre-processing, or the removal of hair and external structures covering the suspected lesion, (2) segmentation of skin lesion for accuracy of diagnosis, and (3) evaluation of the lesion via implementation of the 'ABCD rule' (Thanh et al., 2019). As defined by Kunz and Stolz in a 2018 publication, the 'ABCD rule' is a dermoscopic algorithm for the inspection and identification of melanocytic lesions. The letters of the acronym respectively denote: Asymmetry, Border, Color, and Diameter.

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common form of NMSC among humans, four million cases of which are diagnosed annually in the United States alone. Although keratinocyte carcinomas constitute 99% of all NMSCs, BCC accounts for 80% of all skin cancer diagnoses (Yu et al., 2021). The main histological subtypes of BCC include "nodular" and "superficial" varieties, which account for 63.8% and 14.8% of all BCCs, respectively (McCormack et al., 1997).

Located at the base of the epidermis, basal cells are responsible for the regeneration of cutaneous tissue. Appearance of BCC and its precursor lesions occurs most often on tissues of the head and neck; tumors presenting on mucosal membranes or callused surfaces (soles and palms) are rare, by contrast (McDaniel & Badri, 2019). Whereas intermittent exposure to intense sunlight is the main cause of melanoma, the pathogenesis of NMSC has been linked to chronic UV irradiation (Gloster & Brodland, 1996). Similar to the delay in diagnosis seen with MSCs, clinical onset of BCC manifests 15-20 years after the time of UV damage. However, ultraviolet exposure accounts for only 20% of basal cell carcinomas. Other conditions which predispose a patient to the development of BCC include prolonged consumption of pesticide-contaminated water, radiation therapy (RT), arsenic exposure, tissue scarring, as well as a clinical history of cutaneous disease. Mutations in the *PTCH1*, *P53*, and *CDKN2A* genes are associated with the formation of sporadic BCC tumors (McDaniel & Badri, 2019; Skidmore & Flowers, 1998). Overall, CMM and NMSC differ primarily with regard to prognosis. Malignancies of the basal cells are not as readily metastatic as superficial spreading melanomas. If left untreated, however, BCCs may become locally invasive and infiltrate subdermal tissues adjoining the lesion. Furthermore, postponing treatment of a BCC may increase associated morbidity, risk of recurrence, and in some cases, fatality. As with CMM, the incidence of NMSCs increases with age, lighter skin tone, and exposure to sunlight.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC), the second most common form of cutaneous nonmelanoma neoplasms, is a malignancy arising from the uncontrolled division of squamous cells. These cells, comprising the topmost layer of the epidermis, face extensive exposure to mutagenic

environmental species. Approximately 80% of squamous cell carcinomas manifest in sunlight-exposed tissues of the face, head, and neck region. Conditions associated with an increased risk of SCC are similar to those of metastatic melanoma and BCC; they include traumatic lesions and scarring, prior incidence of cutaneous disease, and exposure to genotoxic substances such as arsenic and cyclosporine (Skidmore & Flowers, 1998). Tobacco smoking, however, is an environmental risk factor unique to SCC (Madan et al., 2010). Compared to BCCs, SCCs have a higher mortality rate, accounting for 75% of NMSC deaths (Gloster & Brodland, 1996).

Diagnostics of MSC and NMSC

Dermoscopic examination remains the primary diagnostic tool in the care and management of skin cancer. Dermoscopy is a non-invasive imaging technique entailing the use of a device known as a dermoscope, which permits the visualization of histological patterns in lesions that are otherwise imperceptible to the naked eye (Schadendorf et al., 2015). In conjunction with molecular and imaging techniques, skin biopsy affords dermatologists with the ability to further resolve whether a lesion is clinically concerning. Biopsies may be classified by the degree to which the suspected lesion is removed. Incisional, or partial biopsy calls for the incomplete removal of the tumor, whereas excisional, or complete biopsy sampling involves resection of the entire neoplasm. Saucerization, or "scoop" biopsy, is the most common excisional technique for the definitive diagnosis of CM. Superficial shave biopsy, on the other hand, may be performed for suspected cases of non-invasive melanoma. However, its use is largely discouraged in the assessment of CM, due to the likelihood of miscalculating the tumor's penetrative ability and consequent malignancy. Roughly 80% of all BCCs occur on the head and neck regions, making clinical diagnosis fairly straightforward. Superficial BCC lesions, in contrast, primarily occur on

the trunk region and are characteristically more difficult to identify. Morpheic lesions, constituting 5% of all histologically confirmed BCC cases, have poorly defined margins and often present at an advanced stage of progression. In a study comparing the accuracy of various diagnostic procedures for NMSC, invasive techniques such as punch and shave excisional biopsies were correct in identifying 81% and 76% of BCC cases, respectively (Bax et al., 2016). Moreover, Grégoire and colleagues (2010) suggested the use of surgical biopsy sampling for pathological confirmation of SCC.

Following biopsy of a lesion clinically suggestive of malignancy, a pathology report is generated. Critical details such as size, maximum tumor thickness (determined via Breslow's staging system for CM), presence or absence of ulceration, mitotic rate (number of dermal mitoses per mm^2), and evidence of malignancy along the peripheral and deep margins are included in the report. Additionally, extent of microsatellite metastasis into the dermis and subcutis, or proximal to the neoplasm and separated by at least 0.3 mm of healthy tissue may be used to indicate the tumor's degree of advancement. Other non-essential details including gross appearance of the lesion, histological class, dermal regression, and evidence of lymphovascular invasion may be provided as well (Swetter et al., 2019). Generally, surgically invasive assessment techniques may afford greater precision in diagnosing lesions presumed to be melanoma.

As the reference standards for accurate identification of NMSC neoplasms, biopsy sampling and histopathologic assessment have been presented as irreplaceable diagnostic and staging procedures (Mogensen & Jemec, 2007). In the last decade, however, minimally invasive technologies have gained greater clinical applicability in the screening and diagnosis of NMSC. As expressed by Ulrich and colleagues (2007), histological evaluation remains the gold-standard

for primary assessment of keratinocyte carcinomas. Other commercially available diagnostic modalities include optical coherence tomography, high-frequency ultrasound and reflectance confocal microscopy. Multiple studies have suggested that simple dermoscopy techniques possess the highest level of efficacy among noninvasive diagnostic tools for the preliminary detection of malignant lesions (Altamura et al., 2010; Ulrich et al., 2007). However, histopathological assessment is required in cases of ambiguous lesions and large or ulcerated tumors for which the diagnosis remains uncertain. Following detection of a malignancy, treatment progress can be monitored via routine clinical evaluation.

Treatment of MSC

For histologically confirmed cases of CM, selecting the appropriate treatment is based on multiple factors. Class, progression, and anatomical site of the lesion primarily dictate the mode of treatment as well as any measures necessary to preempt further progression. In its clinical guideline for the care and management of CMM, the American Academy of Dermatology (AAD) regards surgical resection as the "gold-standard" of treatment (Bichakjian, 2011). These proposed criteria are supported further by Swetter et al.'s (2019) findings that excision remains the primary line of treatment for melanoma *in-situ* (MIS), a subtype of which is known as lentigo melanoma (LM). The rising incidence of larger MSC lesions on medically inoperable sites and in non-resectable patients has necessitated the development of nonsurgical therapy alternatives. Topical treatment modalities and radiation therapy (RT) have thus been proposed for the management of MIS in patients who are not surgical candidates. The use of imiquimod 5% cream for the eradication of LM has presented positive outcomes, both as a primary and adjuvant mode of treatment. As a cautionary note to this approach, specialists warn that nonsurgical

management of LM must be practically deliberated, as noninvasive therapies present the risk of undertreating the occasional case of occult invasive disease within *in-situ* melanoma (Bax et al., 2016). For non-resectable patients, RT has been studied as an auxiliary management option. High cure rates, good cosmetic outcomes, and relatively low recurrence rates (0% to 17%) have been attributed to RT; however, sufficiency of dermal penetration with low-voltage RT is a major concern among healthcare professionals due to the risk of undertreatment (Swetter et al., 2019). A general consensus within the scientific and medical communities calls for the complete excision of melanomas, regardless of aesthetic, financial, and other related implications which accompany surgical treatment.

Surgical Treatment of NMSC

Treatment of basal and squamous cell carcinoma primarily depends on the tumor's dimensions, locus, and histological pattern. As elucidated by Albert et al. (2019), high-risk NMSC lesions requiring aggressive treatment include those located on the trunk or extremities and greater than 20 mm, tumors of the head and neck measuring 10 mm or greater, and those adjoining a free margin (eyelids, nasal cavity, lips, periorbital region) and 6 mm or greater in breadth. While there are several available management options for NMSC, physicians most commonly rely on surgical treatments such as wide local excision (WLE) and closure, cryosurgery, electrodesiccation and curettage (EDC), and Mohs micrographic surgery (MMS) (Fleming et al., 1995). These office-based procedures are decidedly effective, as they have been shown to produce clearance rates ranging from 90-95% (McDaniel & Badri, 2019). Specifically, for large tumors (> 2 cm) and lesions located near a free margin, MMS is the treatment of choice as it allows for increased precision in tumor resection and minimizes the loss of normal surrounding

tissues (Skidmore & Flowers, 1998). Additionally, MMS offers such advantages as superior cure rates and minimal scarring, due to nominal tissue excision. According to a 1995 review of the medical literature, Mohs surgery is most suitable for NMSC lesions occurring in anatomic regions prone to recurrence, large or deeply penetrating tumors, as well as tumors with poorly established margins (Telfer, 1995). Moreover, in support of cryotherapy as a primary line of treatment, multiple studies have underscored its high cure rates (94-99%) and relative affordability (Albert et al., 2019; Bahner & Bordeaux, 2013).

Quality of life outcomes are important considerations in the surgical treatment of typically nonfatal NMSCs. Presently, a variety of surgical procedures offering high cure rates are available for the treatment of keratinocyte carcinomas, particularly if the lesions are found to be neoplastic in their early stages of progression. However, drawbacks associated with these commonly used therapies include poor cosmesis, costliness of surgical procedures, risk of recurrence due to incomplete resection, patient inconvenience and discomfort, as well as the requirement for specialized training of healthcare professionals (Ceilley & Rosso, 2006). Although surgical procedures are most commonly performed to remove NMSCs, financial, patient safety, and quality of life concerns must be addressed prior to selecting this mode of treatment.

Poor Cosmesis

As with any surgical procedure, postoperative complications and excessive bleeding may result following surgical resection of a tumor, especially among immunocompromised and elderly patients (Ceilley & Rosso, 2006). Based on observational studies, the primary anatomic location of NMSC in elderly is the head and neck. In such cases, the cosmetically sensitive locus of the

lesion and general non-resectability of geriatric patients warrant the use of alternative, non-invasive therapies for the care and management of NMSC (Albert et al., 2019). While MMS affords such advantages as reduced recurrence rate and maximal tissue recovery, its labor-intensive quality and associated procedural complications are significant considerations in the realm of post-operative and palliative patient care. Liquid-nitrogen cryosurgery, despite its efficacy and affordability, has been shown to produce adverse effects including moderate-to-severe scarring, erythema, blistering, tissue distortion, and alopecia (Bahner & Bordeaux, 2013). Although aesthetic factors are secondary to the patient's wellbeing, they are nevertheless valid considerations when choosing an effective mode of cancer treatment. Surgical excision requires that both diseased and normal tissues surrounding the lesion be removed to ensure complete resection of the tumor. While such protocol is intended to promote the total eradication of tumorigenic growths, it does not ensure maximal conservation of normal tissues and consequently may lead to anatomic disfigurement. Particularly when resecting BCC lesions, the bulk of which present on cranial surfaces as the head and neck, cosmesis is a pressing concern among patients and specialists alike. While MMS is intended to treat neoplastic lesions located in cosmetically sensitive locations as the face, scarring and aesthetic results may vary, depending on the tumor's dimensions, location, and degree of penetration. EDC, which entails scraping the neoplasm with a curette, followed by electrosurgery to attenuate bleeding and ensure removal of malignant cells from the tumor's circumference, possesses similar disadvantages. One session of treatment is generally insubstantial to fully remove all tumorigenic tissues, and postoperative disfigurement is fairly common among patients. As per Ceilley and Rosso (2006), cryosurgery "is associated with many adverse effects." Aside from postoperative pain and tenderness, local scarring as well as hypo- and hyperpigmentation may result. Analogous to EDC therapy, limiting

the number of cryosurgery cycles to improve aesthetical and functional outcomes may hinder treatment efficacy. Given the adverse effects and poor cosmetic outcomes ascribed to a cryotherapy regimen aggressive enough to eliminate NMSC, this is not a recommended therapy for patients who elect to undergo surgical treatment (Bahner & Bordeaux, 2013).

Risk of Recurrence

Another major concern among surgical professionals is the recurrence of both primary and recurrent varieties of NMSC due to incomplete resection. In such cases, reparation of an excised lesion via WLE and procedural closure, flap, and graft may lead to the masking of remaining malignant cells by induced scars and will thereby complicate identification of the tumor margin (Patel et al., 2017). An estimated 4.7% to 10.8% of treated patients will undergo a BCC excision in which the tumor is not entirely removed. Moreover, recurrence rates ranging from 2% to 8% have been reported in patients treated surgically for the eradication of BCC (Ceilley and Rosso, 2006; Peris et al., 2019). Despite its labor-intensive nature, MMS is intended for tumors at higher risk for recurrence. Some data suggest that recurrence rates are lowest after Mohs surgery, reporting a 5-year recurrence rate of only 1% for primary BCCs removed via MMS. In contrast, significantly higher 5-year recurrence frequencies have been reported for primary BCC lesions resected via EDC (6% to 19%) and cryosurgery (4% to 17%). Moreover, in some cases of cryosurgery, the development of fibrous scar tissue may conceal unresected malignant cells (Ceilley & Rosso, 2006).

Financial Considerations of Surgical NMSC Treatment

On a global scale, the incidence of NMSC continues to rise annually. Presently in the U.S., the yearly cost of treating skin cancer is approximated at $8.1 billion. This cost includes not only physician consultations and treatments, but also the patient's morbidity and time off work (Marks et al., 2001). A report published in the *American Journal of Preventative Medicine* revealed that an estimated 3.5 million cases of NMSC were treated in 2006, in the U.S. alone. Upsurges in the incidence of skin cancer diagnoses occurred between 2007 and 2011, peaking at 4.9 million cases per annum (Guy et al., 2015). According to a 2016 study analyzing the long-term trends in incidence of various skin cancers, NMSCs were projected to cost the UK's National Health Service (NHS) the equivalent of $232 million U.S. dollars by 2020 (Griffin et al., 2016). Because NMSC occurs with greater frequency in elderly patients, Medicare provides cost coverage for most therapies. The estimated annual cost of NMSC care is $426 million for the Medicare population and $650 million for the entire United States (Mudigonda et al., 2010). The recent upsurge in the global number of annual NMSC cases has far-reaching implications. At the core of NMSC therapy is the issue of cost differences in procedure type. Historically, surgical excision of both melanoma and non-melanoma neoplasms has been the primary line of treatment in affected patients. However, the performance of surgery may be affected by various financial considerations. With respect to cost, EDC is the least expensive among available surgical therapies. Costly reconstruction procedures, in turn, may be necessary to diminish postoperative anatomical disfigurement and irregular pigmentation (Chren et al., 2007). Moreover, while cryotherapy is recommended for its ease of use and affordability, the procedure often requires repeated cycles of treatment to effectively remove all malignant tissues. As evidenced by the above figures, the financial burden of NMSC treatment rests both on federal

organizations and individual patients, thereby necessitating the development of alternative cost-effective therapies in NMSC treatment.

MATERIALS AND METHODS

The rising incidence of NMSC has provoked great interest in the discovery of its etiology and the search for innovative, non-invasive treatments. Available evidence published within the past three decades was collected using a systematic search and review of published studies from PubMed and Google Scholar databases from 1995 to 2021. Searches were limited to studies published in the English language. Key search terms included *melanoma, BCC*; *SCC*; *incidence and mortality rates* (*melanoma, nonmelanoma skin cancer*); *financial impact* (*melanoma, NMSC*); *primary treatment* (*melanoma, NMSC*), *surgical treatment* (*melanoma, NMSC*); *Mohs' micrographic surgery*; *electrodessication and curettage*; *excision and closure*; *cryotherapy*; *alternative treatments of NMSC*; *topical creams BCC/SCC*; *anticancer role* (*cannabis, apricots, devil's apple, blackberry seed oil, eggplant, tomato*); *Devil's apple* (*solasodine glycosides, BEC, Curaderm*); *morphologic features* (*BCC, SCC*); *noninvasive diagnostic techniques* (*BCC, SCC*); *alternative/noninvasive NMSC treatments* (*topical imiquimod cream, photodynamic therapy, radiation therapy*).

RESULTS AND DISCUSSION

Nonsurgical Treatments in NMSC

For decades, surgical resection has been the leading course of treatment for both MSC and NMSC malignancies. Nevertheless, the performance of surgery may be impacted by various considerations, including comorbidities of the patient, the anatomical site of the lesion, potential

intolerance for repeated tissue excisions to ensure complete elimination of the cancer, and patient care setting. Moreover, the development of noninvasive treatment modalities has changed the face of NMSC care and management. Commercially available topical therapies including imiquimod, 5-fluorouracil (5-FU), and PDT are presently the mainstay options in the realm of noninvasive treatments, as they may allow for increased drug absorption at the tumor site. Moreover, a cost analysis comparing different NMSC treatments revealed that non-destructive therapies are significantly more affordable than MMS and other traditional methods of surgical excision (Mudigonda et al., 2010). In recent years, FDA-approved anticancer cream formulations such as imiquimod and 5-FU have gained widespread use in the treatment of NMSC.

Imiquimod

Imiquimod, responsible for the synthesis and stimulation of cytokines with antiviral and tumoricidal properties, plays a significant role in immune system modulation. The drug also functions as an antiproliferative agent by blocking the formation of new vasculature vital for tumor growth and recruitment of proapoptotic factors (Desai et al., 2012). Preliminary studies indicate that imiquimod 5% cream is particularity effective in the treatment of superficial BCC, with reported cure rates of up to 94% (Bahner & Bordeaux, 2013). Multiple trials have demonstrated a statistically significant correlation between drug efficacy and dosage. In one study on superficial BCC, 100% clearance was reported for patients treated with 5% imiquimod twice-daily for a period of 3 weeks, while only 89.7% of another cohort, treated once-daily for 3 weeks, responded to treatment (Marks et al., 2001). Across various studies, twice-daily dosing was most effective.

While there are relatively few studies on the treatment of cutaneous SCC using 5% imiquimod cream, cases of successful tumor eradication have been reported. As part of their evaluation of treating SCC with imiquimod 5%, Love and colleagues (2009) reported substantial tumor clearance rates among patients with in-situ (73% and 75%, based on prescribed regimen) and invasive SCC (71%). Imiquimod has also been used as an adjuvant mode of therapy for NMSC. In one study, elderly patients with SCC who were deemed poor surgical candidates experienced 95% clinical clearance after 12 weeks of post-curettage imiquimod application. Regarding the use of topical imiquimod cream, however, Marks and colleagues (2001) reported the occurrence of localized skin reactions in all dose regimens, with erythema presenting frequently. Other common side effects include edema, erosion, scabbing, excoriation (flaking), and ulceration. Albeit rare, "flu-like" symptoms including fatigue, diarrhea, depression, weight loss, and hypotension have been reported in patients undergoing imiquimod treatment. Additionally, the severity of imiquimod application site reactions has been linked directly with dosage strength.

5-Fluorouracil

In contrast to imiquimod, 5-FU functions not as an immunostimulant, but an inhibitor of protein synthesis. As a structural analog of thymine, it can incorporate itself into RNA and thereby halt proteinogenesis as well as induce cell death. Like imiquimod 5%, 5-FU has also been associated with erosion, erythema, and ulceration in a dose-dependent manner. Both imiquimod and 5-fluorouracil are patient-administered. While topically applicable treatments are advantageous on the basis of their affordability and ease-of-use, their use has been discouraged by various healthcare professionals: Inconsistent administration of these topical cream formulations, or other lapses on the part of the patient may render these therapies ineffective.

Radiation Therapy

Due to the radiosensitive nature of BCC and SCC lesions, RT is a yet another treatment option for patients who decline surgery or for whom surgery is not considered a suitable option. Aside from its superior tissue-salvaging capabilities, RT may offer such advantages as improved aesthetic and functional outcome as well as minimal scarring, when compared to simple excision techniques. Radiotherapy is a relatively safe and generally well-tolerated procedure, with high cure rates when performed within prescribed guidelines. Moreover, adjuvant RT was shown to significantly improve relapse-free survival rates in a cohort study of patients with SCC of the head and neck (Veness et al., 2019). One form of RT, known as high-dose electronic brachytherapy (EBT), may serve as an effective mode of treatment for non-melanoma neoplasms. Compared with external beam RT, high-dose rate EBT (contact RT) offers such advantages as maximal preservation of normal tissues, shorter treatment time and improved cosmesis. In a matched-pair cohort study, the cosmetic outcomes of therapy with EBT were compared with those of MMS in patients treated for NMSC. Cosmesis ratings by physicians were "excellent" or "good" in 98% of EBT-treated lesions and 95% of MMS-treated sites. All in all, the results of this study corroborated the existing body of clinical research advocating for the use of EBT in the treatment of NMSC (Patel et al., 2017). High-dose EBT was also found to be a suitable therapy for poor surgical candidates, including older and immunocompromised patients with NMSC (Peris et al., 2019). It is important to note the likelihood of complications such as acute radiation-induced dermatitis, cutaneous erosion, as well as chronic onset of depigmentation and telangiectasia in RT therapy.

According to Madan and colleagues (2010), PDT is presently one of the mainstay nonsurgical treatments for NMSC in the U.S. and Europe. Methyl-aminolaevulinic acid (ALA) is often used

in conjunction with PDT. Topical application of ALA on a lesion prior to PDT administration allows for the accumulation of photosensitive heme precursors. Upon exposure to an appropriate light source and oxygen, cytotoxic reactions will take place within ALA-treated cells. In comparison to cryotherapy and other surgical resection techniques, advantages afforded by treatment with ALA-PDT include improved cosmesis and shorter healing time. However, data show that sBCC clearance rates are minimal with only one cycle of PDT treatment; instead, a minimum of two therapy sessions are necessary (Ceilley & Rosso, 2006). Haller et al. (2000) sought to determine whether a second cycle of PDT one week after initial treatment might improve tumor clearance rates. All lesions treated with two cycles of PDT were successfully eradicated, with an average recurrence rate of 4% 27 months after treatment administration.

Cannabinoids

Cannabinoids (CB) have been utilized in the palliative treatment of a wide range of diseases and pathologic conditions. Due to their analgesic capacity, these compounds are particularly useful in allaying chronic pain and discomfort associated with degenerative diseases such as cancer. Recent studies, however, have demonstrated their antiproliferative, antimetastatic, and proapoptotic abilities in preempting tumor growth. CBs are thought to have antitumor properties, as they interact with essential cellular pathways that are responsible for the viability and proliferation of cells.

CBs may be divided into two categories, endocannabinoids and phytocannabinoids. The former class is endogenous and vital to the maintenance of homeostatic mechanisms throughout the body. Phytocannabinoids and its synthetic derivatives are exogenous compounds derived primarily from the marijuana plant (*Cannabis sativa linnaeus*); they may be used to manipulate

of the endocannabinoid system (ECS) as a means of immunomodulation. The ECS has been credited with the role of regulating inflammatory immune responses and tumor growth within the skin. This immunomodulatory network is comprised of receptors, endogenous cannabinoids, as well as proteins responsible for the production and degradation of the endocannabinoids. The persistence of malignant growths is predicated on the hyperactivity of signaling pathways which regulate cell growth and survival. Pharmacological manipulation of the ECS and its component cell signaling pathways via administration of exogenous, or synthetic CBs such as Δ^9-tetrahydrocannabinol (THC), has been shown to disrupt the uncontrolled proliferation of tumors (Alexander et al., 2009).

In the last two decades, researchers and clinicians alike have increasingly endorsed the use of CBs in the treatment of NMSC. Recent findings have discovered an extensive network of ECB receptor subtypes CB_1 and CB_2 throughout the skin. As per Sheriff et al. (2019), these investigations are collectively suggestive of the existence of an ECS exclusive to the dermis. Additionally, these data have prompted researchers to determine whether the activation of the ECS can indeed preclude the proliferation of malignant cells. One such investigation, performed by Casanova and colleagues (2003), was aimed at evaluating the precise mechanism by which CBs are able to exert antimitotic and proapoptotic effects on malignant cells *in-vivo*. The findings of this study affirmed the *in-vivo* expression of ECB receptors CB_1 and CB_2 in both malignant and non-transformed epidermal cells. The data also indicated that pharmacological stimulation of CB receptors prompted the necrosis of tumorigenic epidermal cells, whereas non-transformed epidermal cells remained unharmed. The primary mechanisms proposed for the regression of skin tumors following CB administration includes direct promotion of apoptotic cell death and inhibition of tumor angiogenesis.

Because endocannabinoid receptors CB_1 and CB_2 are expressed in both melanoma and NMSC cell lines, animal studies have been conducted to assess the antitumor properties of THC, a phytocannabinoid. Investigations showed that activation of CBr_1 and CBr_2 (CB receptors 1 and 2, respectively) in melanoma cells is correlated with elevated apoptotic activity and lowered proliferative ability. The function of CBr_2 was shown to be greater than that of CBr_1 in facilitating the anti-malignancy properties of CB drugs, as the former receptor is primarily expressed in immune system and peripheral tissues while the latter is most active within the CNS. Moreover, when compared to the chemotherapy control, treatment of neoplastic dermal cells with THC exhibited a greater antitumor effect (Sheriff et al., 2019). One 2013 study was conducted to identify potential links between the activation of CBr_1 and CBr_2 and the survival patients with primary SCC. Increased CBr_2 expression in tumor cells was strongly correlated with decreased survivability in patients with SCC of the head and neck. Directions for further study presented the potential promise of utilizing CB receptor agonists in the modulation of CBr_2 immunoreactivity (Nulent et al., 2013). In one recent investigation, CB receptor agonists were shown to attenuate oral SCC proliferation rates and overall tumor viability. Moreover, CBr_2 agonism was shown to be effective as both an analgesic and antiproliferative agent in the treatment of oral cancer. Systemic administration of selective CB_2 receptor agonists may thus serve as a desirable alternative therapy for SCC. CBr_1 agonist administration, however, exerted psychoactive effects in animal studies and possessed little to no antitumorigenic potential (Saghafi et al., 2011). The findings of Zhao and colleagues (2010) further compounded the above data, as SCC tumor cells were shown to overexpress CB_2 receptors, a detail expressive of the receptor's function in SCC tumorigenesis.

It is significant to note that there have been a few reports regarding the pro-proliferative effects of cannabinoids. As per Alexander et al. (2009), lower concentrations of the exogenous CB, THC, have been shown to exert immunosuppressive effects which may in turn promote tumor growth. Nevertheless, a large proportion of researchers are in consensus regarding the function of CBs as inhibitors of angiogenesis. The use of cannabis-derived compounds in the treatment and palliative management of NMSC thereby provides a promising alternative to surgical treatment modalities.

Apricot Kernel Oil (Prunus armeniaca)

For decades, researchers have considered the prospective anticancer properties of apricot (*Prunus armeniaca*). Adachi et al. (2007) examined the antitumor activities of Ume ("*Prunus mume Sieb. et Zucc*"), an apricot variety native to Japan. In this study, the effects of Ume extract were investigated *in-vitro*, on the growth of human promyelocytic leukemia (HL-60) and gastric cancer (Kato-III) cell lines. The data were indicative of the nonviability of cancer cells grown in the presence of Ume extract, thus supporting existing claims regarding the inhibitory effects of apricot varieties on angiogenesis. A 2013 *in-vitro* study was conducted to evaluate and compare the respective antioxidant, antimicrobial, and antitumor faculties of sweet apricot and bitter almond kernel extracts. Collectively, these data delineated the inhibitory effects of sweet apricot and bitter almond on the growth of human breast (MCF-7), colon (HCT-116), and hepatocellular (Hep-G2) carcinoma cells, with variations in treatment sensitivity across the cell lines (Gomaa, 2013). In a number of studies, apricots have demonstrated anticarcinogenic potential, presumably a consequence of their appreciable phytonutrient content. With the aim of characterizing and quantifying the phenolic compound profiles of various apricot cultivars, Ruiz and colleagues

(2005) performed high-performance liquid chromatography (HPLC) analysis of the fruit's extracts. The compounds identified in apricot peel and flesh included procyanidins, hydroxycinnamic acid derivatives, flavanols, and anthocyanins. The apoptotic and anti-proliferative effects of both specimens are attributable to their naturally elevated polyphenol content (Gomaa, 2013). As radical scavengers, phenolic compounds are capable of inhibiting the accumulation of reactive oxygen and nitrogen species in tissues, and thereby preempting the development of various pathologies such as cancer and cardiovascular disease (Rai et al., 2016). Yiğit and colleagues (2009) discovered the *in vitro* antioxidant properties of apricot kernels via quantification of radical scavenging power and total phenolic content. The DPPH assay, commonly used to evaluate the total antioxidant capacity of a compound on the basis of its ability to scavenge DPPH free radicals, was performed. The strong positive correlation between DPPH radical scavenging and phenolic composition ($r = 0.975$, $P < 0.01$) further corroborated existing data on the role of phenolics as antioxidants and consequently, anticancer agents. Further investigations have linked amygdalin (vitamin B-17), a cytotoxic phytochemical occurring in apricots, to the inhibition of angiogenesis. Amygdalin has been shown to exert proapoptotic and antiproliferative effects, in a dose-dependent manner (Chen et al., 2020). Additionally, in minute concentrations, the hydrogen cyanide present in bitter apricot kernels has been shown to exhibit medicinal properties (Yiğit et al., 2009).

Plants of the Genus Solanum

Devil's Apple, or *Solanum linnaeanum*, is a subspecies of nightshade commonly found in the semi-arid regions of southern Africa, multiple Mediterranean countries, as well as New Zealand and Australia. Also referred to as the 'Apple of Sodom,' this plant is renowned for its potentially

fatal effects upon ingestion. However, its potency has led to claims supporting the use of Devil's Apple in the treatment of NMSC. Accounts of the antineoplastic properties of Devil's Apple have been reported particularly among Australian cattle farmers. When crushed and applied to ocular SCC lesions in Hereford cattle, tumors were wholly eradicated. Solasodine rhamnosyl glycosides (SRGs), derived from solanaceous plants such as Devil's Apple and Eggplant (S. *melongena*), have been shown to exhibit antiproliferative activities in the presence of neoplastic cells. BEC is a term coined for the specific mixture of solasodine glycosides present in S. *linnaeanum* and has been used in the care and management of malignant skin lesions. Curaderm, a topical cream formulation containing 0.005% BEC, is used globally in the treatment of NMSCs. *In-vitro* preclinical studies are demonstrative of the selective ability of BEC to eliminate tumor cells while leaving healthy cells unharmed. In several animal studies, direct intralesional injections of BEC were effective in attenuating large tumors (Cham, 2007). In a 2011 study, two cases of NMSCs treated with the topical cream Curaderm were reported. Moreover, two cases of histologically confirmed BCC and SCC, respectively, were subject to treatment with BEC Curaderm. In the first report, a 68-year-old male with a histologically verified BCC lesion of 3 years had declined treatment via surgical resection and reconstruction of the site. Upon treatment with BEC Curaderm, the tumor responded rapidly, and all malignant cells were successfully eliminated from the lesioned site. The latter case study, wherein a 63-year-old patient similarly rejected recommended surgical resection of his facial SCC lesion, demonstrated regression of the tumor after 14 consecutive weeks of Curaderm therapy. No incidences of recurrence were noted in either study and excellent aesthetic end results were reported (Cham, 2011). Topical application of the cream formulation Curaderm should be

considered as a viable alternative to surgical treatment modalities for the care and management of NMSC.

Other members of the genus *Solanum* have also been ascribed with anticarcinogenic capacities. Tomatoes (S. *lycopersicum*) are rich in carotenoids, a class of chemicals known for their protective effects against UV-induced photodamage. In animal studies, tomato extract has been shown to exhibit carcinostatic activities in neoplastic tissues. Koul et al. (2019) sought to determine whether oral administration of lycopene enriched tomato extract (LycT) could inhibit chemically induced skin tumors in mice. LycT was seen to reduce mRNA and protein expression of angiogenic genes, thereby interfering with biochemical processes vital for tumor proliferation. In a similar vein, Cooperstone and colleagues (2017) hypothesized that prolonged dietary consumption of tomatoes could differentially curtail tumor promotion and progression after chronic UVB exposure in male and female SKH-1 hairless mice. Subjects were placed on dietary regimens rich in tomato (approximately 10% tomato) or lacking the fruit entirely. Overall, male subjects that consumed tomato-containing diets demonstrated lower UVB-induced skin tumor presentation rates compared to male mice that did not consume tomatoes. The above *in vivo* studies are demonstrative of the promising anticancer effects of naturally occurring phytonutrients, particularly in the realm of nonsurgical NMSC treatment.

Plants of the Genus Rubus

Approximately 90% of all human NMSCs are attributable to ultraviolet radiation exposure (Mintie et al., 2020). The phenomenon wherein UV-irradiation of the skin prompts development of skin cancer is referred to as photocarcinogenesis (Calvo-Castro et al., 2013). Solar ultraviolet-B (UVB) light has been classified as a complete carcinogen, inducing both the formation and

advancement of skin tumors. Approximately 50% of all UVB induced damage will result in the generation of reactive oxygen species (ROS), responsible for modulating inflammatory responses via activation of mitogen-activated protein kinases (MAPK). The stimulation of MAPK pathways, in turn, is highly attributable to skin carcinogenesis, as unregulated recruitment of proinflammatory cytokines and resultant acute inflammation have been suggested as hallmarks of cancer. NF-κB is another major factor mediating UVB-induced inflammatory responses through the recruit of various proinflammatory proteins. Additionally, the ability of UVB to penetrate the epidermis and induce covalent bond formation between adjacent pyrimidines leads to the generation of mutagenic cyclobutane pyrimidine dimers (CPDs), further increasing the risk of tumor development (Divya et al., 2015). UV radiation's immunosuppressive effects also promote tumor growth by impairing the cutaneous immune response, as elucidated by Desai and colleagues (2012).

To combat the rising incidence of NMSC, educational counseling programs about sun protection have been implemented globally. Despite such initiatives, a need for innovative, noninvasive treatments has risen. Recent studies have elucidated the overall health-promoting and chemopreventative effects of phytochemical and antioxidant-rich fruits. As per Mintie et al. (2015), "*chemoprevention* is defined as the use of natural or synthetic agents to prevent, suppress, or reduce the progression of cancer." Phytonutrients have been shown to act impart protection against carcinogenesis by reducing oxidative stress and inflammation, enhancing repair mechanisms, and improving the skin's function as a barrier against UVB exposure. As secondary plant metabolites, polyphenols comprise a large and diverse group of phytochemicals abundantly present in a majority of fruits, herbs and vegetables. Due to their naturally high polyphenol content, fruits such as the blackberry (*Rubus fruticosus*) and black raspberry (*Rubus*

occidentalis) have been credited with the regulation of biological activities including antioxidant response and angiogenesis. Multiple studies have suggested that topical administration of antioxidants can provide a photoprotective effect and may effectively diminish UVB-induced oxidative damage to primary keratinocytes. Murapa and colleagues (2012) identified over six distinct antioxidants in the 'Hull' blackberry (*Rubus eubatus*) via fractionation of its extracts. Additionally, the three main subtypes of polyphenols in plants of the genus *Rubus* include anthocyanin, ellagitannins, and phenolic monomers (i.e., phenolic acids and flavonoids). The phenolics present in berries possess potent antioxidant, anti-inflammatory as well as antiproliferative properties (Calvo-Castro et al., 2013). Duncan et al. (2009) sought to investigate the antitumor properties of black raspberry extract (BRE), which has been shown to possess carcinostatic properties. UVB exposure of SKH-1 hairless mice, followed by topical administration of BRE, showed reduced levels of leukocyte activity and oxidative DNA damage at the application site, suggesting the inhibition of acute inflammatory responses characteristic of tumorigenesis. In a second carcinogenesis model, topical application of BRE following a similar pattern of UVB exposure resulted in reduced tumor counts and volume, suggesting the antineoplastic faculties of black raspberries. Comparatively, Divya and colleagues (2015) demonstrated the chemopreventative capacities of blackberry extract (BBE) in animal models. When topically applied to SKH-1 hairless mice immediately preceding their exposure to UVB, extract derived from tropical highland blackberries (*Rubus adenotrichos*) was shown to attenuate cellular damage via modulating MAPK and NF-κB signaling pathways and curtailing CPD formation. While exposure of human epidermal keratinocytes to UVB resulted in loss of cell viability, decreased levels of CPD formation and direct oxidative damage were observed in cell cultures (Calvo-Castro et al., 2013). Collectively, these studies are suggestive of the role of

antioxidant and phytochemical-rich species as potent inhibitors of UVB-mediated oxidative injury in primary keratinocytes.

CONCLUSIONS

For decades, surgical resection has been the mainstay course of treatment for both CM and NMSC neoplasms. In addition to improving associated morbidity and mortality of cutaneous cancers, reducing the quality of life and financial concerns associated with surgical therapy is imperative. As this paper sought to demonstrate, the introduction of emerging treatments from the natural product field as well as available noninvasive therapies may have significant implications in the realm of NMSC care and management. Commercially available noninvasive treatments include imiquimod, 5-fluorouracil, radiation therapy (RT), as well as photodynamic therapy (PDT) and are widely used for both their efficacy and affordability. In recent years, cannabinoids as well as topical formulations derived from phytonutrient-rich whole fruit and plant extracts have been considered for use in the primary and adjuvant treatment of non-fatal NMSC. The medical literature has underscored the inherent antitumorigenic properties of such plant species as those of the genuses *Armeniaca, Solanum*, and *Rubus*. In rare cases, lesser proactive measures such as active dermoscopic surveillance have been proposed for non-resectable and elderly patients with NMSC (Peris et al., 2019).

Future Directions

With the advent of innovative NMSC treatments, the risk of tumor undertreatment runs high. While use of the above-mentioned therapies appears promising, due to their appreciable phytonutrient content and proposed antineoplastic properties, further studies are necessary to find

a sufficient quantity of evidence supporting their use. Additionally, this paper merely touches upon the wide scope of plausibly efficacious therapies in the realm of BCC and SCC tumor elimination. I have no doubt that further investigations on alternative NMSC treatments will be equally, if not more, successful.

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