

## A BRIEF REVIEW OF TREATMENT MODALITIES FOR NON-MELANOMA SKIN CANCER

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Received: 05 February 2020, Revised and Accepted: 15 April 2021

## ABSTRACT

NMSC (Non-melanoma skin cancer) is the most commonly occurring malignancy in Caucasians. Out of all diagnosed NMSC cases, 95% of the cases are of basal cell carcinoma and squamous cell carcinoma. The therapeutic approaches to cure or ultimately rescue the skin area affected by NMSC include surgical methods, photodynamic therapy, radiation therapy, immunotherapy, and chemotherapy. This article aims to provide a brief overview of the preliminary mechanism of action, clinical studies, advantages, and disadvantages of currently available treatment modalities.

**Keywords:** Non-melanoma skin cancer, Mohs micrographic surgery, Photodynamic therapy, Chemotherapy, Immunotherapy.

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## INTRODUCTION

NMSC (Non-melanoma skin cancer) is the most common malignancy across the world [1]. NMSC is also known as keratinocyte cancer [2]. As per the American Academy of Dermatology, approximately 9500 people in the United States are diagnosed with skin cancer daily. The Caucasian population is more prone to NMSCs compare to others [3]. Among different NMSC subtypes, BCC (Basal Cell Carcinoma) and SCC (Squamous Cell Carcinoma) are the most commonly diagnosed NMSC, which comprises 70% and 25% cases, respectively [4-6]. Research indicates that more than 3 million Americans are diagnosed with BCC and SCC every year, with an increase of 145% and 263% cases from 2000 to 2010 [7]. These approximations surpass the Caucasians and represent a significant health burden, including morbidity, mortality, and health-care cost. Other much less common forms of NMSC are Merkel cell carcinoma, primary cutaneous B cell lymphoma, Kaposi sarcoma, carcinosarcoma, and dermatofibrosarcoma [8,9].

The most common goals involved in NMSC treatment are complete removal of a tumor to avoid future remission, prevent any functional impairments occurring from tumor removal, and provide the best cosmetic outcome [10]. Accurate evaluation of the tumors' risk and remission chances is essential to determine before initiating treatment to avoid under treatment for the high-risk tumor or over treatment for the low-risk lesion [11]. Different treatment options are available for NMSCs, which include procedural approaches such as standard excision, curettage and electrodesiccation, and MMS (Mohs micrographic surgery). Other approaches include PDT (Photodynamic therapy), topical pharmacotherapy such as 5-Fluorouracil, and IQ (Imiquimod) cream. These approaches are preferred for low-risk NMSCs [12-16]. Recently approved oral therapeutic agent Vismodegib, a selective inhibitor of HH (Hedgehog) pathway activation, is being used for metastatic and locally advanced BCC [17].

This review will cover the available treatment for NMSC, including the primary mechanism of action, the most important clinical studies, and the advantages and disadvantages associated with the treatment approach.

## SURGICAL APPROACHES

## MMS

The concept of surgical removal of cancerous tissue under histologic control is identified as MMS. The technique was established by

Dr. Frederic Mohs. While working, he observed the skin cancer tissue sample from rats treated with an injection of zinc chloride solution. From the observation, he suggested a technique involving controlled *in situ* fixation of patients' cancer tissue by application of complex zinc chloride fixative and abstraction of a fixed layer, segmentation, marking and careful mapping, then the preparation of horizontal frozen histology section allowing analysis of entire margins of removal and identification of the left tumor in tissue. This procedure can be continued until the cancer-free area is achieved. Dr. Mohs named his new surgery technique "Chemosurgery," which states the chemical fixation of surgically excised tissue [18,19]. Over time, the chemosurgery method gained popularity as a treatment option, but it was associated with certain disadvantages such as more than half of a day require to fix the tissue by zinc chloride, the ability of zinc chloride paste to cause significant swelling and pain requiring hospitalization, and duration of each chemosurgery stage (almost a day) resulting in multiple-day treatment. These disadvantages made it unfavorable among patients [20,21].

After a few years, a fresh tissue technique, also known as microscopically controlled excision, was developed. This technique offered several advantages over chemosurgery such as a replacement of zinc chloride with a local anesthetic, immediate processing of excised tumor, and significantly less amount of time for both patients as well as the surgeon. Multiple tissue stages can be achieved in 1 day, and the wound can be reconstructed immediately. This procedure was officially named MMS in 1985 [22]. MMS is the treatment of choice for primary and recurrent BCC located on anatomic sites requiring maximum tissue conservation for routine function. The steps in MMS include biopsy site identification, outline with marking pen, local anesthesia injection, debulking the tumor by scalpel or curette in the saucer-shaped layer, histochemical staining, and microscopic examination [23,24]. The debulking step is repeated until the tumor-free zone is achieved [25]. It has been evidenced that MMS has a cure rate of 99% for primary BCC [26]. In terms of recurrence, the chances of recurrence are 5.6% with MMS, which is 17.6% for standard excision, 9.8% for radiotherapy, and 40% for curettage and desiccation [27].

Out of all available surgical approaches, MMS is the most preferred due to the long-term cure rate and less pain compared to other approaches [28]. The current MMS technique employs optimal margin control and conservation of healthy tissue [29-31]. MMS technique provides high cure rates due to the complete evaluation of the deep and peripheral surgical margins using frozen sections [32]. The physician

functions as both the surgeon and pathologist for the MMS, ensuring integrated, precise removal of the tumor without significant errors introduced by involving other persons' judgment. Reconstruction is done after tumor-free surgical margins are ensured with a 100% margin evaluation [33]. In MMS thin layers of tissue are taken only from the area of positive tumor margin, which minimizes the wound size and provides the superior outcome. In most cases, restoration of the defect after the surgery can be done on the same day. However, MMS has disadvantages such as long surgical treatment period, inability to perform the surgery on patients who cannot tolerate surgery under local anesthesia, and difficulty in clearing margins for aggressive tumors involving deep structures, such as bone or parotid gland [18]. Complication like difficulties in homeostasis is associated with the MMS [10].

#### Standard surgical excision (SSE)

SSE is the inpatient clinic procedure, performed under the influence of local anesthesia. It involves egg-shaped surgical removal of the tumor, and the surgical defect is closed side by side. In this technique, the variable amount of tissue is forfeited to achieve acceptable cure rates. The excised tissue is then fixed in formalin, embedded in paraffin, and stained to inspect margins microscopically [34]. SSE with predetermined margins has provided a 5-year cure rate of over 98% for BCC and 92% for SCC [35,36]. SSE has been linked with the histologic analysis of the excised tissue; hence, presence of tumors can be confirmed. Sometimes SSE leads to infection and hematoma formation. SSE has been linked with a high recurrence rate due to the absence of a complete surgical margin assessment [10].

#### Curettage and electrodesiccation (C and D)

The use of electrodesiccation for skin cancer started in 1911 when Clark [37] observed superficial tissue drying on the application of high voltage low current to the skin through a mono-terminal electrode [37]. Dermal curette usage started in 1870 by Piffard [38]. Several years later, Wigglesworth reported the use of curette in various dermatological conditions such as Psoriasis and Syphilitic Condylomata [39]. In 1906, Fox introduced the Fox model of a curette, which is the most famous curette model until now [38].

In this technique, the lesion is infiltrated with the local anesthesia to perform the biopsy, followed by a visible tumor is electrodesiccated and then curetted to remove the central portion of the tumor. It is easy to remove the central part of the tumor using this technique, but precautions should be taken when the procedure is being used to remove the peripheral portion of the tumor to avoid recurrence. The number of C and D cycles depends on tumor location [40]. C and D technique is widely used for the treatment of benign and selected malignant cutaneous neoplasm. C and D are used for low-risk BCC and SCC but not used for high-risk BCC due to a high recurrence rate [10,41-45]. The success rate of C and D has been entirely dependent on the physician's experience. 5-year cure rate obtained after C and D of primary, non-fibrosing BCCs of medium and high-rank areas of the face having a size <1 cm when operated by a skilled surgeon is 98.8% [46]. However, it has been observed that as the size increases to 2 cm or more, the cure rate was reduced to 95.5% and 84%, respectively [47]. The use of C and D has been widely praised and also severely criticized. C and D are considered as a reasonable, least expensive, and fastest method among all treatment approaches for NMSC [10,45]. The disadvantages associated with C and D are more care required for the generated wound and a slower healing rate. It often produces a white atrophic scar, which is unacceptable by the patient and also results in the recurrence of high-risk BCC [45].

#### CRYOTHERAPY

Cryotherapy involves the continuous application of liquid nitrogen ( $-196^{\circ}\text{C}$ ) to the tumor and a small surrounding area [48] till the temperature of the skin reaches  $-60^{\circ}\text{C}$  measured by inserted temperature probe [10]. During the freezing cycle with subzero temperature, the tumor site undergoes sloughing of the damaged tissue,

followed by healing. The subzero temperature causes cellular changes resulting in cell death. It is recommended that at least two freeze-thaw cycles of 40–60 s are required for the destruction of malignant lesions, including BCC [49]. Cryotherapy can be used for low-risk BCC but not for high-risk BCC due to the high recurrence rate. Sometimes, it is combined with curettage, known as curettage and cryotherapy [10]. A systemic review of the recurrence rate for 27 years indicated that cryotherapy has a recurrence rate of 4–17% [50]. It is maybe because there is no histologic confirmation of tumor-free area after cryotherapy [49].

The advantage associated with the therapy is the low-cost procedure for low-risk NMSC when the patient cannot undergo radiotherapy or surgery [10]. The success rate of the treatment is operator-dependent. Cryotherapy requires an extended healing time compared to the sutured wound. The overall relapse rates are high for primary and recurrent BCC [26,27]. In cryotherapy, the patient experiences pain and swelling after the treated area is thawed. The pervasive adverse effects are pigment loss, atrophy, and hypertrophic scarring. Motor and sensory neuropathies are uncommon adverse effects.

#### PDT

The non-invasive photodynamic treatment involves the use of light, oxygen, and photosensitizer [6,51]. On exposure to light from the monochromatic or polychromatic light source, the photosensitizer undergoes a photochemical reaction, which generates singlet oxygen species ( $^1\text{O}_2$ ) and other ROS (Reactive oxygen species) having the capacity to kill the cancer cells [52-55]. The anti-tumoral effect arises from three principle mechanisms; direct cytotoxicity on cancer cells, indirect impact as a consequence of damaged tumor vasculature, and activation of the immune response [51]. Principle compounds used in PDT are ALA (5-Aminolevulinic acid) and its MALs (Methylated derivatives).

ALA is applied topically or administered systemically. In the cytosol, ALA is taken up by enzymatic equipment of heme synthesis and converted to PPIX (protoporphyrin IX), a substance essential for photosensitizing activity. On exposure to light, PPIX absorbs the provided photo energy and initiates molecular electronic transition leading to photodynamic reactions. These reactions produce ROS and bring out cancer cell death [56-62].

As per the research done by various groups, it has been proven that PDT is effective in treating superficial BCC, SCC, and AK (actinic keratosis) but it is not currently recommended for invasive SCC and aggressive BCC [14,15]. A retrospective study published by Christensen *et al.* [63], in which 44 BCC patients, with 60 histopathologically confirmed BCC lesions, were treated for 6 years with ALA PDT. This treatment resulted in the complete remission of the lesion in 81% of the patient population [63]. Wang *et al.* performed a Phase III study comparing the effect of ALA PDT with cryosurgery on 88 patients with basal cell epitheliomas. On analysis, it was observed that ALA-PDT provides a similar result to that of cryosurgery with the advantage of a better cosmetic outcome [64]. Apart from this, a study performed evaluating the effect of PDT on nevoid BCC syndrome (Gorlin-Goltz syndrome) concluded that blue light-activated topical 20% ALA at a fluence rate of 10 mW/cm<sup>2</sup> for 1000 s is efficient in managing Gorlin-Goltz syndrome [65,66].

Apart from ALA, MAL is also a very safe and efficient PDT molecule being used in the management of BCC and SCC. Soler *et al.* [67] published a study in which the therapeutic effectiveness of MAL was analyzed on 350 superficial BCC lesions. On application, complete remission in more than 85% of the lesion was observed, and 89% of them were able to maintain remitted status for more than 3 years with good or excellent cosmetic outcomes [67]. MAL-PDT is also efficient in treating lesions present at challenging to treat positions such as periorificial, nasal region, auricular pavilion region, or the region having potential chances for developing surgical complications or in patients who are on anticoagulant therapy or at cardiovascular disease risk [68]. Similar to ALA, MAL is also efficient in treating patients suffering from

Gorlin-Goltz syndrome [69]. Moreover, PDT can also be combined with other treatment modalities such as electrosurgery, lasers, IQ, 5-FU (5-fluorouracil), IM (ingenol mebutate), and topical retinoids for NMSC treatment [51]. PDT is also useful in reducing the incidence of AK and SCC in patients who are on long-term immunosuppressive therapy due to organ transplants [14,15]. PDT has tolerable side effects such as pain, burning sensation, erythema, edema, and low cost make PDT more favorable [10].

#### RADIATION THERAPY

Radiation therapy is another approach to treat NMSCs since the 1900s, but the use was declined after the development of MMS [70]. However, with the advancement in technology resurgence in radiation therapy has been observed, identified as SRT (superficial radiation therapy) [71]. It is being used as primary therapy and/or adjuvant therapy for NMSC [10]. There are three methods currently used for radiation therapy, which are orthovoltage or superficial X-ray, megavoltage, and brachytherapy. Orthovoltage range from 75 to 125 kV and is used when tumor thickness is <5 mm. More commonly used megavoltage therapy uses an electron beam of 6–20 MeV strength and is capable of penetrating tissue up to 6 cm. Brachytherapy uses a radioactive substance, which is applied on the surface or is placed interstitially [72]. In brachytherapy, energy is imparted on rapidly dividing tumor tissue to inhibit mitosis [71]. In a retrospective analysis performed by Schulte *et al.* [73], in which SRT was used to treat a total of 1267 NMSCs with an overall dose of 6100 unit gray (cGy) for BCCs and 6360 cGy for SCCs in a dose fractionation manner for either 3 times/week or 6 days/week. Patients were examined for a mean duration of 6.5 years. A recurrence rate of 5.1% was found for all NMSCs combined [73].

The advantage of external radiotherapy is that the maximum dose of radiation can be targeted to the skin surface, and it is less likely to penetrate through eye shields, which makes it favorable to use around the eyes [74]. Radiotherapy is preferred in cases where the patient disagrees with the surgical procedure, the surgery likely to compromise the vital function, or the surgery is contraindicated due to medical reasons. On the contrary, radiotherapy is an expensive treatment requiring 15–30 clinic visits to reduce poor cosmetic results by fractionizing the dose. Radiation therapy is contraindicated in patients suffering from xeroderma pigmentosum because they risk impairing DNA damage repair by ionizing radiation [75–77].

Radiotherapy is associated with complications such as desquamation, alopecia, atrophy, pigmentary changes, telangiectasia, fibrosis, ectropion, parotitis, buccal mucositis, tooth loss, gingivitis, and a loss of salivary glands are associated with the use of radiation therapy. Moreover, severe complications such as soft tissue or bone necrosis, cataracts, conjunctival scarring, or eyelid deformity are linked to radiotherapy [78].

#### CHEMOTHERAPY AND IMMUNOTHERAPY

Systemic chemotherapy has a key role in the management of advanced, metastasized NMSC, inoperable lesions due to size and location, patient age, and general medical condition likely to cause functional impairment if treated by excision [79]. Different topical formulations containing 5-FU, IQ, IM, retinoids are being used for the management of BCC. Selected immunomodulators belonging to the class of EGFR (epidermal growth factor receptor) inhibitors such as Cetuximab and Panitumumab can also be used since EGFR is also involved in the pathogenesis of SCC [80,81]. Systemic drugs like Vismodegib are another drug used in the treatment since the involvement of the HH in the NMSC progression. Newer therapies are developed that target PD-1 (Programmed death-1) immune checkpoint receptors and ligands. Anti-PD-1 antibodies are found to be useful to patients who have failed to respond to smoothened inhibitors such as Vismodegib and other chemotherapeutic agents such as Paclitaxel and Cisplatin [82].

5-FU is the standard treatment modality for AKs from 1960 [83–85]. It is available in different concentrations ranges from 0.5% to 5% for the

disease management. It is an antimetabolite, which binds to thymidylate synthase and inhibits the conversion of deoxyuridine to thymidine nucleotides. The reduction in nucleotide synthesis leads to a decrease in DNA, and RNA synthesis leads to decreased cell proliferation and apoptosis [85–87].

5-FU is used in a condition where multiple lesions are involved, lesions present at the difficult-to-treat site, in a condition where surgical and other conventional methods are not approachable [88–90]. There are multiple clinical studies done to analyze the efficacy of 5-FU against NMSC. The result of the clinical study, where 31 patients having superficial BCCs were enrolled and treated with 5% 5-FU twice a day for up to 8–12 weeks, showed complete histological clearance of tumor in 90% of the cases [88]. The efficacy of 5-FU has also been tested in nodular BCCs, which was found to be less [91,92]. The use of 5-FU in SCC treatment is off the label with variable efficacy. In one open-label study, 26 histologically confirmed SCC lesions were treated with 5% 5-FU twice a day for 9 weeks resulted in complete clearance in 92% of the patients [93].

The use of 5-FU in the treatment of NMSC is extensive, but it is associated with concentration-related adverse events such as erythema, blistering, necrosis, erosion associated with pruritus, and burning associated with skin reactions [85,86,94]. Treatment with 5-FU is contraindicated in patients with a deficiency of dihydropyridine dehydrogenase responsible for the degradation of 5-FU and pregnant women [95].

IQ is an imidazoquinoline amine approved by the FDA (Food and Drug Administration) in 1997 for the management of external genital and perianal warts. IQ is an immune response modifier, which interacts with Toll-like receptor seven located on the surface of antigen-presenting cells and modulates both innate and acquired immunity [96–98]. IQ has been reported to have apoptotic and anti-angiogenic properties [99]. It is available in topical formulation ranging from 2.5% to 5% concentration.

In a meta-analysis performed by Hadley *et al.* [100], IQ 5% cream was applied twice a week for 16 weeks in patients suffering from AKs in comparison with placebo. After the treatment for 16 weeks, complete clearance was observed in 50% of the population [100]. In a randomized control trial, 128 patients were divided into four different groups based on treatment frequency, twice daily, once daily, 5 days/week, and 3 days/week application. After 12 weeks of treatment, IQ treatment showed 100, 87, 81, and 52% histological tumor clearance. Out of all, 5 times a week, treatment provided the best results in terms of efficacy and the least side effects [101]. In a recent randomized clinical trial, where clinical efficacy between IQ, 5-FU, and PDT was compared in 601 patients and provided treatment of IQ (once daily for 5 days for 6 weeks), 5% 5-FU cream (twice daily for 4 weeks), and two rounds of PDT (1-week gap in between two successive rounds). After 12 months, the tumor-free percentage was 83.4%, 80.1%, and 72.8%, respectively [102].

IQ has been reported to cause moderate to severe local skin reactions such as pruritus, burning, erythema, erosions, exudation, hypopigmentation, and crusting. Conjunctivitis and keratitis are likely to occur when IQ comes in direct contact with the mucosal surface during periocular lesion treatment [102]. The use of topical steroids is contraindicated with IQ as it may cause a reduction in clinical efficacy. The patient should avoid exposure to sunlight after IQ application as it may cause sunburns [96].

IM is a macrocyclic diterpene ester obtained from a plant extract of *Euphorbia peplus*. IM causes cellular death in the treated area within a few hours of topical application. IM causes direct cell necrosis by mitochondrial swelling and chemoablation of the plasma membrane. Along with this, it also produces an inflammatory response through protein kinase C activation, which induces the elimination of residual cells [103]. IM is being used for BCC treatment, but its use is off the label

with excellent results [104,105]. The application of IM is associated with erythema, skin flaking. In some cases, it has been reported to cause blistering, swelling, erosion, ulceration. The skin responses are intense after the application, but it becomes mild and gradually disappears after 2 or 4 weeks [106,107].

Retinoids are Vitamin A derivatives, which are capable of influencing the growth and differentiation of epithelial tissue by interacting with specific cellular and nuclear receptors [108], and as a result, retinoids can control cell proliferation and differentiation, which may promote apoptosis [109]. About 0.1% Tazarotene gel was evaluated for BCC in a clinical study involving 20 patients with superficial and nodular tumors, and it produced a complete response in 53% (11 of 13 superficial and 5 of 17 nodular lesions) of the cases after applying once a day for 8 months [110]. Retinoids may cause mild to moderate erythema, peeling dryness, burning, and pruritus.

### SYSTEMIC CHEMOTHERAPY

Systemic targeted chemotherapy is an essential therapeutic approach when NMSC is in the advanced or metastasized stage. Antifungal agents have been explored as NMSC treatment because of their efficacy in inhibiting the HH pathway. Itraconazole and posaconazole have shown their effectiveness against NMSC, but their adverse effects made severe questions regarding their usage in clinics [81,111]. Vismodegib is another agent having the capacity to inhibit the sonic HH pathway and was approved in 2012 but become less favorable due to its serious adverse events [112].

Vismodegib is a synthetically derived oral inhibitor of the HH signaling pathway. This pathway is only active during embryogenesis and has a crucial role in cell growth and differentiation. In BCC, the upregulation of this pathway is due to the mutation of the PTCH (Patched 1) tumor suppressor gene, which inhibits the signaling activity of a seven-transmembrane protein, that is, SMO (smoothed homolog). Inhibition of SMO signaling resulting in activation of glioma-associated oncogene family of zinc-finger transcription factors resulting in aberrant pathway activation and uncontrolled cell proliferation of keratinocyte [17]. Vismodegib binds and inactivates SMO resulting in suppression of downstream production and proliferation factors resulting in tumor suppression [17]. A multicenter, international, two-cohort, non-randomized study evaluating safety and efficacy of vismodegib (150 mg daily for around 7.6 months) in 104 enrolled patients suffering from metastatic and locally advanced inoperable BCC was done. The result of the study concluded a 30% response (with no complete response) (according to RECIST (Response Evaluation Criteria in Solid Tumors) guideline) in 33 patients having metastatic BCC while in 63 patients suffering from locally advanced BCC, the response rate was 43%. In this clinical trial, less than half of the patients experienced adverse events such as muscle spasms, alopecia, dysgeusia, weight loss, and fatigue [113].

Cetuximab is a chimeric Immunoglobulin G1 antibody, which is approved by the FDA for the treatment of locally advanced or metastatic SCC of the head and neck, having the capacity to inhibit EGF receptor. EGFR overexpression is associated with the activation of intracellular tyrosine kinase, which further activates multiple downstream pathways leading to cell survival, angiogenesis, and cell proliferation [114]. Cetuximab can also be administered as an intravenous infusion in combination with cisplatin or 5-FU [114].

There have been few clinical studies assessing the response of cetuximab in unresectable and inoperable SCC. In an open-label, uncontrolled, multicenter Phase II clinical study evaluating the effect of cetuximab as first-line treatment for 6 weeks in 36 patients with unresectable SCC showed disease control in 69% of the patient according to the RECIST criteria [115]. In a comparative treatment study where five patients were treated with cetuximab with radiotherapy, nine patients with carboplatin, and six patients with cetuximab alone for 2 months

resulting in 80%, 37.5%, and 33% response rate, respectively [116]. Treatment with cetuximab is associated with relatively low side effects [117].

### CONCLUSION

NMSC is the most common skin cancer in the United States. As per the American Academy of Dermatology, more than 3 million people are affected by NMSC every year in the United States with an annual estimate of the 4.8 billion dollars financial burden for treatment. There are multiple therapeutic approaches available for NMSC treatment. Out of all treatment modalities, MMS is considered the most preferred one to the patients as it provides a complete cure or a very long disease-free survival period. Apart from MMS, C and D, cryotherapy, and SSE are also used as treatment modalities, but associated unwanted effects and disease relapse rate makes them less favorable. PDT is also one of the potent approaches for the NMSC. Several studies have proved the effectiveness of PDT against SCC and AK. Research also indicates that PDT, in combination with chemotherapeutic agents like 5-FU provides more cancer cell death compared to single treatment alone. Systemic chemotherapy or immunotherapy is considered favorable approaches in conditions such as the inability of surgical approaches to treat patients, patients having advanced disease states, and high-risk BCC or SCC. Patients having multiple NMSC tumors with indistinct boundaries are treated by topical chemotherapy containing IQ and 5-FU. Vismodegib, a HH pathway inhibitor is also useful in NMSC treatment, but it is associated with a severe adverse event. A recently newer therapeutic approach like anti-PD-1 antibodies is efficacious in cases where therapies such as vismodegib, paclitaxel, or cisplatin have failed to provide relief in advanced and high-risk NMSC.

### AUTHOR CONTRIBUTION

HS is responsible for writing and editing the manuscript.

### CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interests.

### FUNDING SOURCE

The author received no specific funding for this work.

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