Integrated Management of Cutaneous Squamous Cell Carcinoma

Subjects: Dermatology

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Cutaneous squamous cell carcinoma (cSCC) is one of the most prevalent neoplasms worldwide. Important risk factors for cSCC include sun exposure, immunosuppression, pale skin, and aging. White people are more likely to develop cSCC, and men are more affected than women.

cutaneous squamous cell carcinoma | metastasis | management | skin cancer

1. Introduction

Despite the increasing prevalence of cutaneous squamous cell carcinoma (cSCC), global numbers remain underestimated [1][2]. In the last three decades, the incidence of cSCCs has increased from 50% to 300%, and their prevalence in European countries is projected to double by 2030 [3]. In the Caucasian population, the probability of having cSCC at any point in life is believed to be between 7% and 11% [4]. Five-year cure rates of typical indolent cSCC are >90%. Advanced cSCC is defined as locally advanced or distant cSCC. Metastatic cSCC is a very small part (3–5%) of cSCC [5]. cSCC still carries a considerable burden on overall mortality due to its high frequency [6].

2. Management

2.1. Surgical Options

2.1.1. Excisional Surgery

Surgical excision is the most effective option for removing the tumor entirely. It is an outpatient procedure in low-risk cases with a faster recovery time. It allows for tissue histologic assessment and cure rates of up to 95% for some primary cSCCs [7]. The recommended free margin of normal skin is 6–10 mm for high-risk cSCC and 4–6 mm for low-risk cSCC [8][9]. To ensure complete tumor removal, extirpated specimens must be forwarded to an experienced surgical dermatopathologist for meticulous margin evaluation. For lesions with high-risk characteristics or those regarded as very high-risk, doctors recommend broader margins of at least 15 mm [10] to ensure complete tumor elimination. Such enormous margins are only possible in a few body regions with sufficient cutaneous laxity to tolerate such enormous defects. In addition, instead of routine surgical excision, high-risk tumors should be referred to Mohs surgeons for Mohs micrographic surgery (MMS), which allows for proven tumor removal without the requirement of extensive wide margins of normal cutaneous areas.

2.1.2. Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) is a surgical procedure that enables a complete microscopic view of the tissue, the accurate determination of positive tumor margins, and total tumor clearance. Because surgical excision with negative margins is linked to considerably reduced recurrence rates, MMS is the benchmark for the surgical eradication of high-risk cSCC as it offers high cure rates and low recurrence rates [11][12][13]. MMS cure rates for primary cSCCs are 97%, and 94% for recurrent cSCCs [12][14]. Recent studies have demonstrated that MMS is highly effective in treating high-risk cSCCs and avoiding local recurrence [15][16]. A multidisciplinary team may be required to ensure total clearance in complex advanced cases with bony infiltration, parotid gland involvement, perineural spread, or metastases. MMS is a more precise and efficient method as compared with conventional surgical excision [17]. The fixed formalin paraffin embedded (FFPE) technique involves the storage of tissue samples to preserve tissue morphology and cellular integrity. Despite the usage of formalin, a toxic and time-consuming protocol that precludes the widespread application of the technique, the combination of MMS with FFPE provides more reliable results [18]. Restaging with data acquired by Mohs surgery is far superior to staging with biopsy data alone, as the surgeon performing the surgery can recognize high-risk features not identified on focal biopsy specimens [19]. Low-risk cases of cSCC can also be offered the option of MMS, where it is available after considering the cost. Patients of cSCC who undergo conventional surgical excision and in turn have positive margins can be referred to a Mohs surgeon for further surgical planning. If margins are positive on Mohs surgery, then this should be discussed in a multidisciplinary board meeting. If the perineural invasion is observed during MMS, then additional radiotherapy should be added to the post-operative care plan [11].

2.1.3. Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SNLB) can potentially improve screening for metastasis, prognostication, and patient selection for early therapy and adjuvant clinical trials. However, most international standards do not endorse SNLB. In a meta-analysis of 19 studies, a positive sentinel lymph node was found in 12.3% of the 130 patients with cSCC who underwent SLNB, and the false-negative incidence was 2.6%. In those with a positive node, the primary cSCC diameter was >2 cm. Sentinel lymph nodes were negative in all nine patients with T1 lesions in whom the tumor had been confined to the mucosa (0%) as per American Joint Committee on Cancer (AJCC) criteria. Positive nodes were present in 3 of 5 patients with T4 lesions in whom the tumor had spanned through all layers of the tissue (60.0%), and in 13 of 116 patients with T2 lesions in whom the tumor had spread into the submucosa (11.2%). No patients with T3 lesions were enrolled in the study [20]. A recent systematic evaluation reported an SLNB positivity of 13.9% with a false-negative rate of 4.6% [21]. In another review of 23 studies with 566 patients examined, the proportion of patients with cSCC and positive SLNB was 8% [7], which was lower than that observed in previous analyses [20][22]. There were insufficient numbers of participants in the investigations to confidently establish the determinants of SLN positivity [23]. The actual clinical value of applying SLNB in patients with cSCC has not been clearly defined. In addition, information on the prognostic value of SNLB remains insufficient for recommending its routine use in patients with cSCC. Surgery could still be offered after a multidisciplinary consultation with a restricted group of patients. More effort should be made to identify the predictors of sentinel lymph node involvement for effective patient selection.

2.2. Targeted Therapies

2.2.1. PD-1 Inhibitors

Neoplastic cells can interact with some immune cells and alter their activity. Co-receptors operate as both activators and inhibitors of the host response when a host body identifies the antigen produced by the human leukocyte antigen (HLA) complex in the tumor cell [24]. cSCC has one of the most significant mutational defects of any cancer, making it a favorable candidate for immunotherapy [25]. Immune checkpoint inhibitors are effective against tumors with a high mutational burden [24][25]. The higher risk of cSCC in immunocompromised patients emphasizes the important role of the immune system in the growth of cSCC [26][27]. Therefore, clinical trials of these remedies for the treatment of cSCC have been conducted.

Immune checkpoint receptors include inhibitory receptors like programmed cell death 1 protein (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA4). T-cells, B-cells, natural killer cells, monocytes, and dendritic cells express the inhibitor co-receptor PD-1 [28]. This transmembrane protein interacts with receptors on the surface of tumor cells, PD-L1 and PD-L2. Binding triggers a signal that suppresses active T-cells and results in immunological enervation via anergy and T-cell apoptosis [29][30]. Using monoclonal antibodies to target immunological checkpoint proteins has resulted in therapeutic benefits for cancer patients [31][32][33]. Proliferating cells and the tumor microenvironment make up an established tumor. Both the tumor stroma and the inflammatory infiltrate constitute the latter. To improve the immune response, most immune checkpoint inhibitors target lymphocytes in the TME [28][29][30][31][32][33][34].

The PD-L1/PD-1 axis is a fundamental modus operandi of malignant immune circumvention and has been the main concept behind developing novel treatments in recent years. PD-1 inhibitors have been developed for a variety of cancers. However, because of the limited response of cSCC to other systemic treatments, medications targeting this axis are effective in some patients [35][36]. These preliminary findings require a more thorough investigation of this approach and its possible therapeutic significance in cSCC. Surface PD-1/PD-L1 has been found in several malignancies. Its expression has been associated with poor clinical outcomes [37][38], including cSCC [39][40][41][42].

Cemiplimab was the first drug approved by the FDA and EMA to treat advanced cSCC. The FDA approved cemiplimab on 28 September 2018 for patients with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma [43]. Cemiplimab also received conditional marketing authorization for the same indications valid throughout the European Union on 28 June 2019 [44]. It is a PD-1-targeting human monoclonal antibody. It has been proven successful in immunocompetent patients with metastatic disease (RR 47%) and advanced cSCC (RR 50%) [43]. Cemiplimab is now being investigated as neoadjuvant therapy in patients with recurrent stage III-IV head and neck cSCC before surgery (NCT03565783) and as a preoperative intralesional injection in patients with recurrent cSCC (NCT03889912).

Pembrolizumab was also authorized by the FDA on 24 June 2020 for advanced cSCC as it showed encouraging clinical benefit and durable responses. Pembrolizumab efficacy was investigated in the KEYNOTE-629 trial, and it

was approved for metastatic or recurrent cases of squamous cell carcinoma that are not curable by surgery or radiation [45]. Presently, immune checkpoint inhibitors are the standard of care in metastatic and locally advanced cSCC. Several clinical trials are also ongoing to manage advanced cases of cSCC with intra-lesional instillation of cemiplimab or in neoadjuvant or adjuvant scenarios after surgery and radiotherapy, as well as research on pembrolizumab. In culmination, the anti-PD1 agents cemiplimab and pembrolizumab are approved by the FDA for the treatment of advanced cSCC. Presently, immune checkpoint inhibitors are the standard of care in locally advanced and metastatic cSCC [43][44][45][46].

The most common adverse effects of immune checkpoint inhibitor (ICI) are diarrhea and fatigue, both of which are relatively minor adverse reactions. Immune checkpoint inhibitors are known to cause minor inflammation; therefore, in patients with pneumonitis, colitis, hepatitis, thyroiditis, or hypophysitis, it is necessary to take them carefully. These unwanted reactions can be severe in some instances, requiring termination. Dermatitis and pruritus are other possible side effects [47].

In addition to clinical trial evidence, multiple case reports of immunotherapy effectiveness in immunocompetent cSCC patients have been published [48][49][50][51]. The utilization of checkpoint inhibitors is an obstacle for transplant patients because increased T-cell activation can galvanize allograft rejection [52]. As transplant cases are frequently omitted from clinical studies, data are scarce, and only data from isolated cases are accessible [50][52][53].

On 21 January 2021, cemiplimab was removed from France's list of reimbursable medicine specialties in view of the absence of phase III randomized trials demonstrating comparative or higher efficacy of cemiplimab versus other systemic treatments [54]. However, patient support programs are available in the United States of America. These programs assist eligible patients with medicine-related out-of-pocket expenses and reimbursements. They also provide cemiplimab free of cost to eligible patients who are uninsured [55]. Nonetheless, a research study has even observed that cemiplimab is a cost-effective use of payer resources for treating advanced cSCC and provides value for money from a healthcare payer's outlook [56].

2.2.2. EGFR Inhibitors

EGFR inhibitors have been documented for advanced cSCC, with most trials focusing on cetuximab, which has a lot of heterogeneity and a small number of patients. Cetuximab can be used in combination with radiotherapy or chemotherapy [57]. Contemporary international clinical guidelines recommend cetuximab in cases that fail to respond to or have contraindications for immune checkpoint inhibitors [46]. EGFR has been identified as a key therapeutic target in various tumor types. Blocking EGFR signaling using monoclonal antibodies or small compounds is effective. In cSCC, EGFR expression is frequently dysregulated [58]. In contrast, gefitinib and other EGFR tyrosine kinase inhibitors have demonstrated only a limited therapeutic effect in patients with cSCC [59].

2.2.3. Cytotoxic Agents—Chemotherapy

Polychemotherapy with cytotoxic agents such as carboplatin, 5-fluorouracil, methotrexate, bleomycin, and gemcitabine have been employed as off-label chemotherapy in advanced cSCC. Recent guidelines state that these

systemic chemotherapies can be used only in cases that fail to respond or are intolerant to anti-PD-1 immunotherapy [46].

2.2.4. Novel and Upcoming Treatment Agents and Targets in Development

Antibody-drug conjugates are a new type of anticancer treatment that combines the selectivity of targeted therapy with the deadly efficacy of chemotherapy medicines [60]. Another interesting way to target antigens is to go after cancer stem cells or tumor-initiating cells [61].

MicroRNAs (miRNAs) are a group of RNAs that have a crucial gene-regulatory role. Many studies have proved that dysregulation of these microRNAs is linked with developing many neoplasms. Flotillin-2 is an essential lipid raft component that is usually positively associated with oncogenesis. Nevertheless, it has demonstrated that Flotillin-2 expression cSCC was low. In addition, Flotillin-2 is a direct target gene of microRNA. Flotillin-2 plays an anti-oncogenesis role in cSCC. MicroRNA miR-486-3P acts as an oncogene in cSCC through the mitigation of Flotillin-2. This is an exciting novel target for the treatment of cSCC [62].

2.3. Adjuvant Treatment for High-Risk Patients

Adjuvant treatment is recommended for high-risk cSCC because of recurrence, metastasis, and disease-specific mortality. While there are several alternatives for therapy before surgery, there is little agreement on the appropriate perioperative management [63]. For local or high-risk cSCC with negative margins, substantial perineural, more extensive, or identified nerve involvement or other high-risk characteristics, the National Comprehensive Cancer Network guidelines advocate for multidisciplinary consultation and adjuvant radiotherapy (RT). Its use is justified by the prospect of lowering the risk of local recurrences. In patients who have repeated excisions that are not feasible after surgical excision for cSCC with positive margins, European guidelines propose postoperative RT [64]. According to a previous study, the benefits of adjuvant RT following cSCC resection with negative surgical margins are questionable [65].

According to the British Association of Dermatologists (BAD) guidelines, adjuvant RT should be offered to patients with incompletely excised cSCC who cannot undergo further surgery and have an increased risk of local recurrence. Adjuvant RT is recommended for T3 tumors that have been completely excised and meet the high-risk criteria. Post-operative RT should be avoided in patients with completely resected T1 or T2 cSCC [66].

2.4. Radiation Therapy

For high-risk cSCC, radiation therapy is employed as a primary therapeutic option because of its noninvasive nature [67]. It cures a broad spectrum of cSCC types, including aggressive ones with lower cure rates. Radiation therapy is as effective as surgery for malignancies in the lips and eyelids [68][69]. A rigorous treatment regimen requires dedication. At the same time, it allows for the histological confirmation of tumor margins [70]. Furthermore, radiation therapy is recommended in individuals who are poor surgical candidates, who have tumors in inoperable locations, or whose reconstruction may have cosmetic or functional ramifications. In tumors that have failed to

respond to other treatments, radiation therapy alone is most commonly employed as salvage or palliative therapy [71].

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