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Use of Cemiplimab in Locally Advanced Cutaneous Squamous Cell Carcinoma

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Abstract

Background: Cutaneous Squamous Cell Carcinoma (cSCC), is one of the major types of skin cancer, along with basal cell cancer and melanoma. It usually presents as a hard lump with a scaly top but can also form as an ulcer. The greatest risk factor is high total exposure to ultraviolet radiation from the sun. Squamous cell carcinomas are generally treated by surgical excision, Mohs surgery or electrodessication and curettage. Non-surgical options for the treatment of cSCC include topical chemotherapy, topical immune response modifiers, Photodynamic Therapy (PDT), radiotherapy, and systemic chemotherapy.

Patient and Methods: The patient was a 92-year old female with cSCC at the left side of frontal bone, which was removed a few times by surgery. In July 2018, a last attempt at removal was made, R2 resection with penetration versus meningeal tissue. She was irradiated in this area with 70Gy, achieving reduction of the tumor mass and relief. In May 2018, upon tumor progression, cemiplimab (Libtayo) treatment was suggested.

Results: After 6 cycles of treatment, more than 50% tumor reduction (as shown by MRI) was seen, along with partial healing of wounds caused by bone destruction. Adverse effects appeared with a cutaneous rash, Grade IV, after the 5th cycle, treated successfully with prednisone.

Conclusion: The use of Cemiplimab is safe and effective and needs to be considered as a first-line treatment in such cases.

Keywords: Advanced squamous cell carcinoma; Surgery; Radiation therapy; Cemiplimab

Introduction

Cutaneous Squamous Skin Carcinoma (cSCC) is one of the most common skin cancers, second to Basal Cell Carcinoma (BCC). Non-Melanoma Skin Cancer (NMSC) is known as the most common type of cancer in Caucasians. Both tumor entities show increasing incidence rates worldwide, with stable or decreasing mortality rates [1]. NMSC is an increasing worldwide problem for health care services due to significant morbidity [2]. Approximately 9,500 people in the US are diagnosed with skin cancer every day. Current estimates are that one of five Americans will develop skin cancer in their lifetime. According to the latest literature, about 700,000 new cases of non-melanoma skin cancer, including basal cell carcinoma and squamous cell carcinoma, are diagnosed in the United States each year [3,4]. The main risk factors are UV irradiation and immunosuppression [5]. SCC cancer tends to appear after many years of sun exposure on the skin, especially head, neck and dorsal aspect of the hands. In women, SCC can be found frequently on their lower extremities. Other possible locations can be the oral cavity, lips, and genitals [2,5].

The appearance of SCC can be indicated by a bump or lump on the skin that can feel rough, as the bump or lump grows, it may become dome-shaped or crusty and even bleed; flat, reddish, scaly patches that grow slowly (Bowen's disease); A sore that does not heal, or heals and returns. Most SCC can be eradicated by surgery [6]. Standard excision with conventional permanent (i.e., paraffin-embedded) tissue sections is a highly effective and well-tolerated therapy for primary cSCCs that lack high-risk features and are in areas where tissue sparing is not critical. Surgical excision offers histologic verification of tumor margins, rapid healing, and improved cosmesis [7]. Mohs micrographic surgery (Mohs) is a specific technique for removal of vast forms of skin cancer, including cSCC. Due to its numerous advantages, Mohs is the gold standard treatment in the following situations, SCC with the need for tissue preservation, ill-defined SCC, high-risk SCC and recurrent tumors. Electrodessication and curettage could be an alternative treatment for low-grade cSCC on the trunk and extremities.

Radiation therapy as primary treatment for cSCC is reserved for patients who are not candidates for surgical excision due to medical conditions, or as an adjuvant treatment in cases of positive margins after resection, to improve locoregional control. Postoperative radiotherapy is considered in cases of perineural invasion or other high-risk features and for those tumors that involve regional metastasis [8].

There are no comparative studies of surgery versus surgery plus adjuvant radiotherapy for high-risk SCC. Due to lack of evidence of benefit, clinical judgment is required for decisions of which patients should receive adjuvant radiation. In a systemic review, Rudkin et al. suggests that adjuvant radiation in patients should be performed in questionable or advanced nerve involvement or positive surgical margins [9].

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The use of Photodynamic Therapy (PDT) is also mentioned in cases of locally non-advanced SCC. PDT achieved high efficacy in the treatment of T1N0 cSCC with greatly reduced morbidity and disfigurement. The technique is simple, carried out in outpatient clinics, and is highly acceptable by patients [10].

In case of high-risk SCC or metastatic disease, various chemotherapeutic agents have been used. These agents have an established role in chemotherapy for mucosal head and neck SCC; however, the data is insufficient for cSCC. The most common non-targeted agents used in cSCC are carboplatin, 5-FU, cisplatin and taxanes [9]. Cetuximab, a monoclonal antibody that inhibits EGFR, demonstrated successful results in multiple case reports, but without enough evidence-based studies [11]. In a small number of patients, SCC can be incurable due to local progression or metastatic disease, despite radiation therapy and surgery. It is agreed that this incurable situation should be considered for a palliative therapy.

Migden et al. recently published a Phase II clinical trial using cemiplimab, (LIBTAYO®; cemiplimab-rwlc), a human programmed death receptor-1 (PD-1) monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death ligands 1 (PD-L1) and 2 (PD-L2) [12]. The drug received approval in the USA for the treatment of patients with metastatic or locally advanced cSCC in September 2018. In this report, we describe our experience with the treatment of local advanced cSCC in a female patient treated with cemiplimab.

Case Report

A 92-year old female, in relatively good condition for her age, came to our department in February 2017, after removal of SCC from the skin of the frontal bone on her left side. The resection margins in histology were positive but, in consideration of her age, irradiation was avoided. She did not return for follow-up, despite our requests. She was re-operated in September 2017 and again in July 2018. The last procedure included a large resection that destroyed the frontal bone, leading to penetration of the tumor to the brain. Following the surgery, she was sent to Radiation Therapy and was treated with 70 Gy in August 2018. The irradiation treatment reduced the tumor mass. In May 2019, she came to our clinic again, this time with a locally advanced tumor, destroyed frontal bone and intra-cranial involvement. After approval from the local Institutional Board, we began therapy with intravenous cemiplimab 350 mg every three weeks. MRI was performed before the first and after the fifth treatment. Clinical photos of the tumor lesion were also taken for follow-up.

Results

The treatment was well tolerated. The only adverse effect was a skin rash and itching grade IV, after five treatments that was treated with Prednisone 80 mg for 5 days, with very good results. Massive reduction (more than 60%) of the tumor was seen on MRI, and in the photos (Figures 1 and 2). On MRI prior to treatment, T1-weighted image showed a hypointense, enhancing, large mass involving the left sphenoid wing, protruding into the orbit and medially pushing the lateral rectus muscle and eyeball with the left eye proptosis. The tumor process exhibited a low signal on ADC maps, suggestive of a hypercellular mass. Follow-up MRI after three months showed a significant volume decrease of the lesion (Figure 3). Furthermore, enhancement of the mass appeared less intense and more heterogeneous and peripheral, possibly as a sign of necrosis.

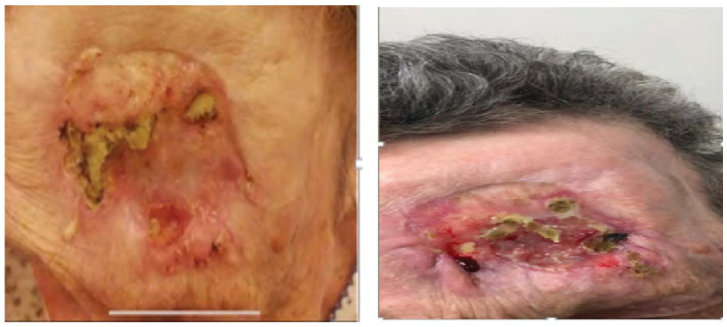

Figure 1: A: Before treatment; B: After 5 treatments.

Figure 2: A: T1 before and after contrast injection; B: Diffusion-weighted imaging (DWI)) before treatment.

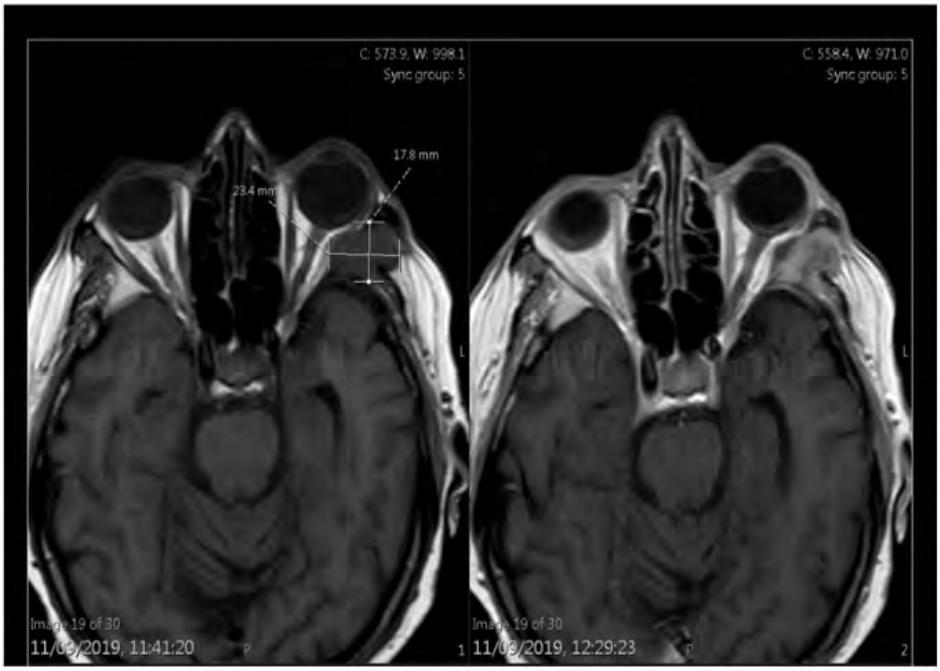

Figure 3: Follow-up MRI after 3 months showed a significant volume decrease of the process. Furthermore, enhancement of the mass looks less intense and more heterogeneous and peripheral, possibly as a sign of necrosis.

On MRI before treatment, T1-weighted image showing a hypointense, enhancing, fairly large mass involving the left sphenoid wing, protruding into the orbit and medially pushing the lateral rectus muscle and eyeball with left eye proptosis. The process exhibits a relatively high signal on DWI and low signal on ADC maps, suggestive of a hypercellular mass.

Discussion

SCC in an advanced phase is a life-threatening condition. Various systemic treatments, especially chemotherapy, have failed. Rudkin et al. found that the use of topical 5-FU 1% is effective as adjuvant therapy prior to surgical excision in cases of localized ocular surface squamous neoplasia [13]. The addition of chemotherapy to high fractionation radiation therapy, in cases of advanced head and neck SCC, demonstrated improved overall and progression-free, cancer-specific survival, without a significant increase in high-grade acute and late toxicities [14]. As mentioned earlier, the main treatment of SCC is surgery, accompanied by radiation therapy [6-9]. Incurable SCC is estimated at between 3900 to 8700 patients a year in the USA [15]. In Israel, the estimation, according to the Israeli Tumor Registry, is 60-80 patients a year [16]. Due to the very high cost of treatment, we also examined the economic and ethical aspects of the treatment. It appears that, despite the patient's advanced age, there was a marked improvement in her condition following treatment with cemiplimab and, from an advanced nursing status, she became partially independent in most ADL (Activities of Daily Living) functions. Therefore, our report indicates that the treatment not only extended life but added "healthy years of life" to our patient.

Cognitive impairment has a harmful effect on quality of life and is associated with functional limitations and disability in older adults. Physical activity has shown to have beneficial effects on cognition [17]. In our case report, as mentioned above, the clinical improvement brought the patient to partial independence in most ADL functions. Cutaneous SCC carries a low, yet significant risk of metastasis and death [18]. Patients with cSCC had a 3.7% risk of metastasis and a 2.1% risk of disease-specific death. Tumor diameter of at least 2 cm, invasion beyond fat, poor differentiation, perineural invasion, and ear, temple or anogenital location were associated with poor outcomes. Accurate risk estimation of outcomes from clinical trials and population-based data proving the utility of disease-staging modalities and adjuvant therapy is required. Cemiplimab showed good results in 13/26 patients in a Phase II study, with relatively not severe adverse events. Although the costs of medical care and social compensation for the patient were lower than the cost of cemiplimab treatment, the authors believes that values of such treatment, and so called "health" and "well-being" should not be estimated based on costs only. This case report supports the need to include cemiplimab, despite its price, in the list of technologies provided by the state to its citizens ("basket of drugs"). Treating with immunotherapy earlier in the course of cancer progression can provide significant value, despite having a substantial budgetary consequence.

Conclusion

Our case report showed a massive tumor reduction, with adverse effects of itching and cutaneous rash, developed after five treatments, and controlled with steroids. The use of cemiplimab is safe and effective and needs to be considered as a first-line treatment in such cases.

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