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Case Report

Treatment of Head and Neck Cancer with Photodynamic Therapy with Redaporfin: A Clinical Case Report

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Keywords
Head and neck cancer · Immunotherapy · Immune checkpoint Inhibitor · Photodynamic therapy · Redaporfin

Abstract
Advanced head and neck squamous cell carcinoma, after locoregional treatment and multiple lines of systemic therapies, represents a great challenge to overcome acquired resistance. The present clinical case illustrates a successful treatment option and is the first to describe the use of photodynamic therapy (PDT) with Redaporfin, followed by immune checkpoint inhibition with an anti-PD1 antibody. This patient presented an extensive tumor in the mouth pavement progressing after surgery, radiotherapy, and multiple lines of systemic treatment. PDT with Redaporfin achieved the destruction of all visible tumor, and the sequential use of an immune checkpoint inhibitor allowed a sustained complete response. This case is an example of the effect of this therapeutic combination and may provide the basis for a new treatment modality.

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Introduction

More than 630,000 new cases of head and neck cancer are diagnosed each year worldwide. Multimodal treatment of head and neck cancer involves surgery, radiotherapy (RT), and chemotherapy (CT). However, disease recurrence is common, and most patients cannot be salvaged with additional anticancer treatment. For these cases, photodynamic therapy (PDT) can be an appealing alternative, since there is no tissue resistance or exposure limitation to its use, and head and neck cancer can be accessible to direct irradiation [1]. PDT is also as effective as conventional therapies for the treatment of early (Cis, T1, T2) squamous cell cancers of the head and neck [2].

PDT is performed using a photosensitizer followed by its photoactivation by a light of specific wavelength in the presence of oxygen to generate singlet oxygen and reactive oxygen species. The accumulation of cytotoxic reactive oxygen species in the treated areas leads to tumor cell death via apoptosis or necrosis, resulting in tumor destruction [3].

Redaporfin (laboratory code: LUZ11; chemical designation: 5,10,15,20-tetrakis [2,6-difluoro-3-*N*-methylsulfamoylphenyl] bacteriochlorin) is currently being developed by Luzitin, S.A. (Coimbra, Portugal), as a new photosensitizer for PDT of solid tumors, with which irradiation is feasible by direct illumination or via endoscopic means. Redaporfin was specifically designed to minimize the risk of photosensitivity, to have a deeper activity in the tumor mass, and to achieve an improvement in efficacy/safety compared to the approved photosensitizers for systemic use (i.e., porfimer sodium, Photofrin®; temoporfin, Foscan®) [4]. Redaporfin has obtained orphan drug designation by the EMA and FDA for the treatment of cholangiocarcinoma [5, 6]. Checkpoint inhibitors are approved for the treatment of cisplatin-resistant recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) by outperforming standard-of-care CT and inducing durable responses in a subset of patients [7].

The combination of PDT and specific immunotherapy agents is an appealing approach and can efficiently eradicate established tumors [8]. Herein, we describe a patient with locally advanced HNSCC progressing after surgery, external beam RT, and CT who was treated with Redaporfin PDT followed by an immune checkpoint inhibitor (ICI), nivolumab. This case illustrates the efficacy of PDT with Redaporfin in patients with HNSCC and suggests a potential role in combination with an ICI.

Case Report

A 62-year-old man with a history of heavy smoking habits and professional exposure to industrial solvents and metal dust was diagnosed with a SCC of the mouth floor. A head and neck computed tomography scan showed a lesion of the mouth floor with bone destruction, stage cT4N2bM0 (AJCC/TNM v7). Treatment with RT/CT (RT was delivered using 70 Gy in 35 fractions [6 MV] and cisplatin 40 mg i.v. weekly) was completed in July 2012 with stable disease. Due to local progression, palliative CT with carboplatin, paclitaxel, and cetuximab (paclitaxel 80 mg/m^2, carboplatin AUC 2, and a cetuximab 400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly) was started in October 2012. Cetuximab was suspended in July 2013 after a grade 3 infusion-related reaction (CTC AE v4). Considering the partial response obtained, CT was stopped in April 2014, and palliative maxillofacial surgery (sequestrectomy and mandibular osteotomy) was performed on May 14, 2014. Local progression was diagnosed in September 2014, and the patient was re-challenged with weekly carboplatin and paclitaxel, with stable disease as best response. Due to progressive disease, weekly

methotrexate (40 mg/m^2 i.v.) was started in September 2015, without relevant response. In March 2016, a clear increase in the submental lesion was identified with ulceration of the oral cavity, and CT was suspended. Magnetic resonance imaging (MRI) on April 16, 2016, showed a large mass centered in the mental region with the largest diameter being 52 mm, with probable invasion of the subcutaneous fat, skin, and tongue associated with bilateral cervical lymphadenopathy. The patient presented a good performance status, with ECOG 1. On April 28, 2016, best supportive care or inclusion in a clinical trial was proposed.

After signed informed consent had been obtained and the screening procedures had been completed, the patient was successfully included in a clinical trial to investigate tolerability and to identify the effective dose of Redaporfin in patients with advanced head and neck cancer (EudraCT 2013-003133-14; NCT02070432). On May 2, 2016, according to the study protocol, the patient was submitted to an exploratory PDT session with Redaporfin 0.75 mg/kg comprehending only a small fraction of the tumor (1-cm-diameter circle in the tumor surface) (Fig. 1a), which was illuminated with a 749-nm laser light dose (50 J/cm^2). Figure 1b depicts the results at 72-h posttreatment. Following this PDT session, an evident antitumoral effect on a well-defined area of necrotic tumor tissue was observed, coincident with the laser illumination; this area became mummified and was detached 5 days later. There were no immediate study-related adverse events. No signs of photosensitivity were observed on the skin photosensitivity tests performed before the patient was discharged. Considering these results, a first PDT session with treatment intent was performed on July 19, 2016. After intravenous administration of Redaporfin 0.75 mg/kg, 2 distinct areas of the tumor with 3.2 cm diameter each were illuminated (Fig. 2). After this PDT treatment, due to an incidental and unauthorized prolonged period of direct sunlight exposure, the patient developed a grade 3 (CTC AE v4) photosensitivity reaction with edema of the face/head and hands, followed by hyperpigmentation and desquamation of the affected areas. Systemic steroids and local skin emollients were able to quickly and completely resolve the situation after 6 days.

An evident area of necrosis in the PDT-treated areas was evident by clinical physical examination. Therefore, a new Redaporfin PDT session with treatment intent was performed on September 19, 2016, to complete the destruction of the remaining tumor mass (Fig. 3). After this procedure, a marked reduction in tumor burden due to detachment of necrotic tissue and regenerated skin tissue was observed in the areas previously occupied by tumor, and a clear objective response to PDT treatment was possible to be determined on physical exam (Fig. 3).

The overall Redaporfin safety and tolerability profile was favorable. The patient completed the last per-protocol evaluation on October 31, 2016, and was referred back to the usual treating physician. On November 1, 2016, a biopsy confirmed a relapse in the border of the nonilluminated area with a spot of malignant cells. The patient was re-challenged with palliative CT with methotrexate from November 2016 to February 28, 2017, but imagological progression was observed.

Based on the promising results of preclinical studies conducted by our group on the combination of PDT with Redaporfin and nivolumab [9] and published data showing that PDT may induce immune response [8], we decided to propose the patient for treatment with nivolumab (3 mg/kg, every 2 weeks), which was started on March 30, 2017, after "exceptional use authorization" by the Portuguese medicines agency (INFARMED). In addition, partial surgical removal of the right-side exposed mandible bone was performed. Sustained complete clinical response was observed after 33 cycles of treatment with nivolumab. The last radiological evaluation with MRI, in April 2018, did not reveal unequivocal tumor progression; however, the T2 signal was heterogeneous and compatible with inflammatory changes, so that it was not

possible to exclude persistence of the tumor. There was no suspicious involvement of the oral mucosa, submucosa, and cervical lymph nodes (Fig. 4).

During the last observation, on June 16, 2018, the patient was on treatment with nivolumab, without any adverse event related to present or previous therapies, presenting good performance status (ECOG 1) and sustained clinical complete response.

Discussion/Conclusion

PDT is considered as effective as primary surgical resection for the treatment of early-stage SCC of the oral cavity, and it is a valid function-preserving approach to treatment according to the published literature [10]. PDT is also effective against the overall management of oral premalignant lesions [11]. Palliative treatment with temoporfin PDT seems to increase the quality of life in otherwise untreatable patients [12]. However, temoporfin shows marked photosensitivity complications and requires very demanding light exposure restrictions [13]. The molecular characteristics of Redaporfin, especially the light wavelength range at which Redaporfin is photoactivated, are associated with high efficacy, lower risk of photosensitivity, and less strict light conditions, which creates an opportunity to treat patients with head and neck malignancies, including cases with advanced disease [14–17]. This case illustrates that PDT sessions with Redaporfin can be repeated in order to achieve maximal destruction of the targeted tumor. The use of PDT and ICI has been described in the literature [18]. The strategy employed in this patient of combining Redaporfin PDT and ICI can become a new option to successfully treat resistant HNSCC, improving outcomes and prolonging survival. The authors are interested in further collaboration and updated cases or trials comprehending the combination of PDT and ICI.

Statement of Ethics

This study (EudraCT Number: 2013-003133-14) was approved by the National Ethics Committee for Clinical Research. Written informed consent was waived by the same committee.

Disclosure Statement

The Experimental Pathology and Therapeutics Group from the Portuguese Institute of Oncology, Porto, Portugal, received investigational grants for preclinical studies from Luzitin, S.A.

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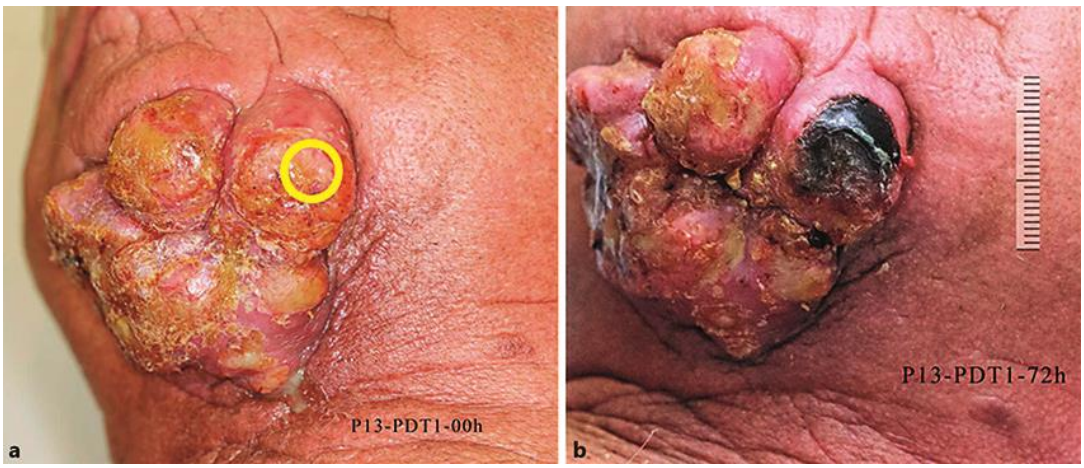

Fig. 1. Clinical evolution of the illuminated area during the dose-finding phase: only a small fraction of the tumor was targeted with laser light (1-cm-diameter circle of tumor surface) after i.v. administration of Redaporfin 0.75 mg/kg (procedure performed according to the clinical trial protocol). **a** Pre-dose. **b** 72 h after photodynamic therapy.

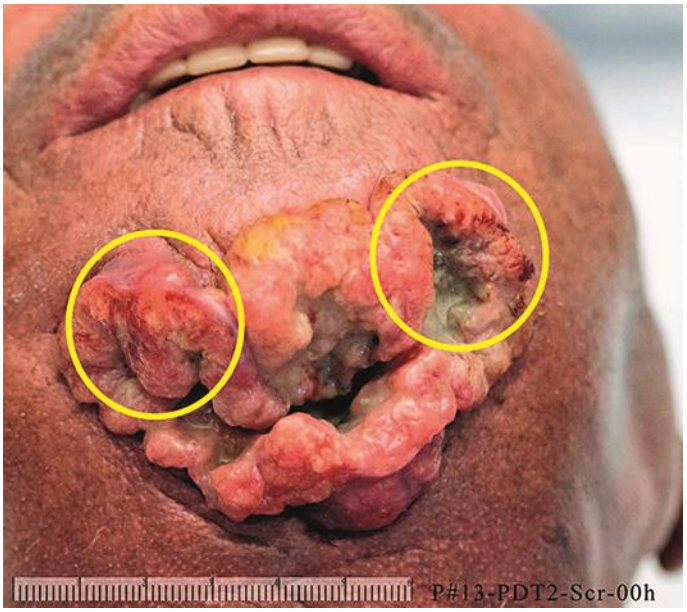

Fig. 2. Identification of the 2 illuminated tumor areas before the first photodynamic therapy session with treatment intent: 3.2-cm-diameter tumor spots were targeted with laser light after i.v. administration of Redaporfin 0.75 mg/kg.

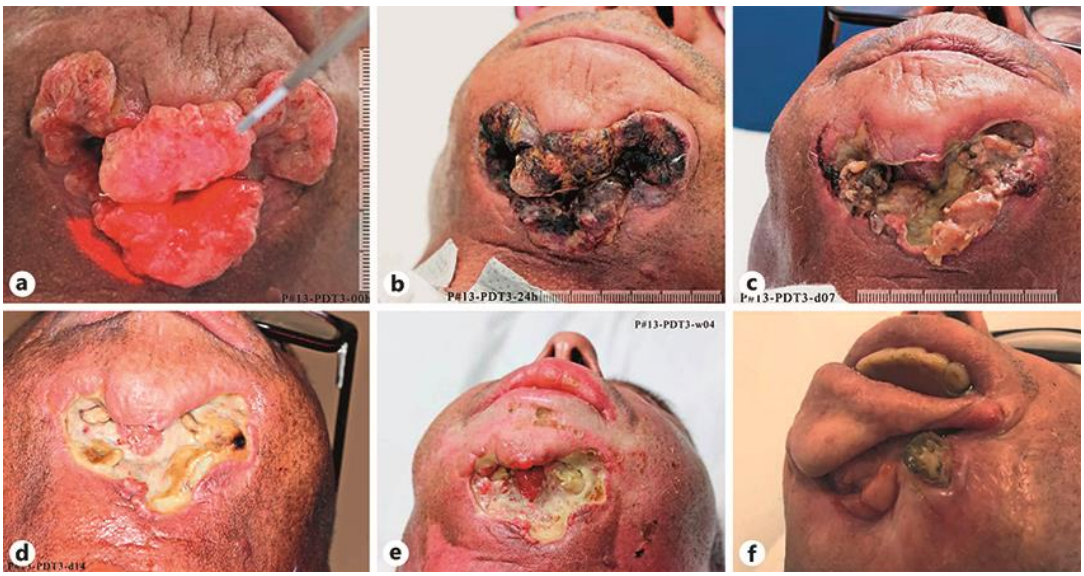

Fig. 3. Clinical evolution of the 4 illuminated tumor spots, with a 3-cm diameter each, after perfusion with Redaporfin 0.75 mg/kg, in the second PDT session with treatment intent. **a** Pre-dose. **b** 24 h after PDT. **c** Day 7 after PDT. **d** Day 14 after PDT. **e** Day 28 after PDT. **f** 19 months after PDT. PDT, photodynamic therapy.

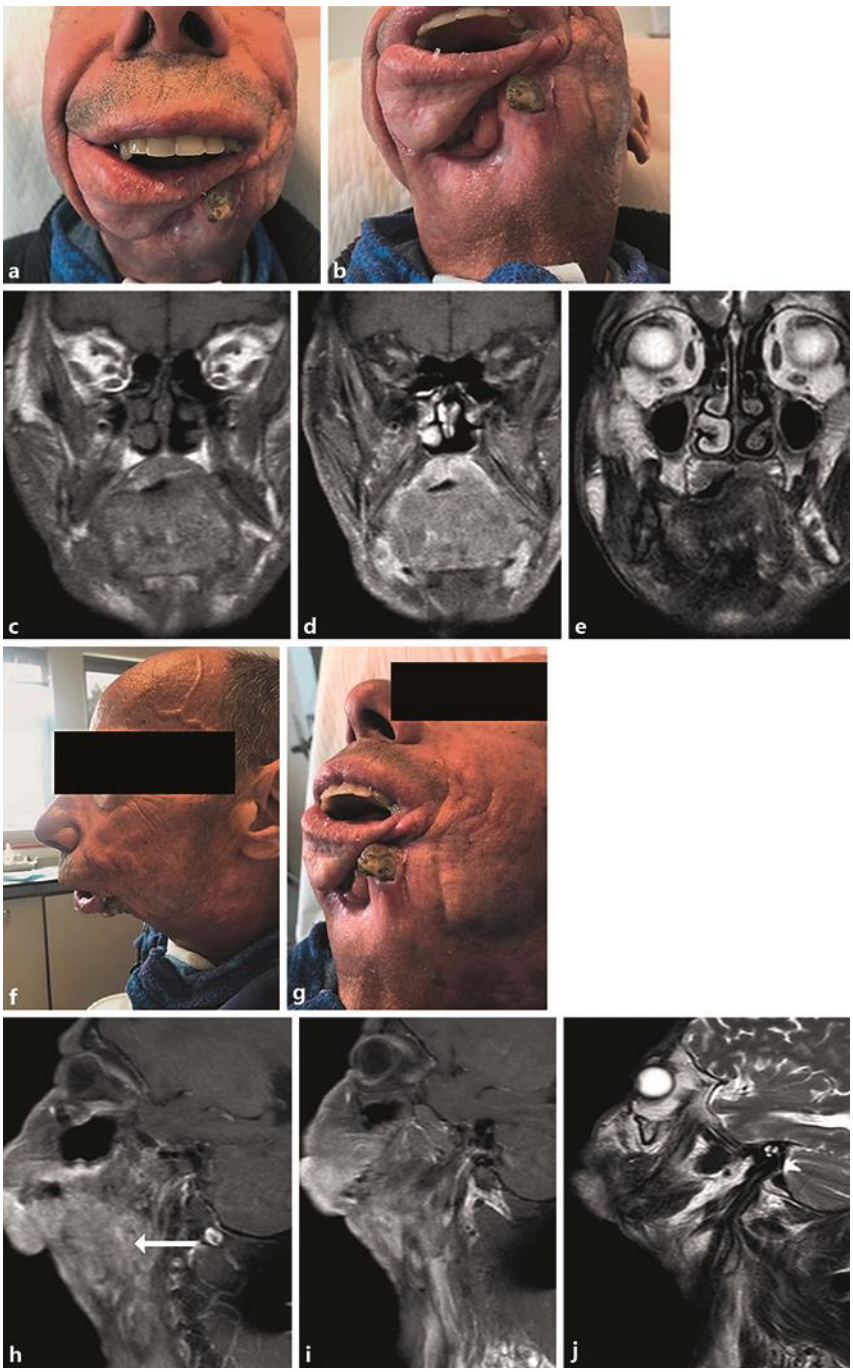

Fig. 4. Patient photograph on the day the last evaluation with MRI was performed, in April 2018 (**a**, **b**, **f**, **g**). The patient presented clinical complete response; there was ongoing treatment with nivolumab, started on March 30, 2017. MRI revealed a diffuse-uptake area involving the anterior third of the tongue with extension to the soft tissues (**c**, **d**, **e**, **I**, **j**); the arrow in **h** points at a heterogeneity of the T2 signal, which is compatible with inflammatory changes; however, the presence of a tumor component could not be excluded; there was no suspicious involvement of oral mucosa, submucosa, and cervical lymph nodes. MRI, magnetic resonance imaging.