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A Spectacular Response to the Docetaxel Cisplatin Fluorouracil (TPF) Protocol as Induction Chemotherapy in Locally Advanced Squamous Cell Carcinoma of the Lower Lip: A Case Report

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Abstract **Case Report**

Background: Oral-mucosal squamous cell carcinoma (omSCC) is a substantially more aggressive disease that affects the oral mucosa, tongue, floor of mouth, and oropharynx, where it is estimated that between 18.6% and 44% of patients present with nodal disease depending on the subsite. As the lip is a site of anatomical overlap, primary squamous cell carcinoma of the lip (lip SCC) exhibits higher rates of nodal spread, mortality, and poor clinical outcome compared with cutaneous SCC. For patients with locally advanced OSCC, rapid advancements regarding the choice of induction chemotherapy regimen have been made. There is substantial evidence related to the advantage and superiority of three-drug combination of Docetaxel, Cisplatin, and Fluorouracil (TPF) over the doublet regime of Cisplatin and Fluorouracil (PF) used previously as induction chemotherapy (ICT). **Case *presentation*:** A 54 years Moroccan women old, who has been accusing, for more than a year, of a neglected painful tumefaction of the lower lip. The clinical examination finds a budding and ulcerous tumefaction of the lower lip and a biopsy of his lip lesion was scheduled. Histopathology report poorly differentiated squamous cell carcinoma. Assessment of extension showed bilateral cervical lymphadenopathy and no distant locations. After a multidisciplinary discussion, the decision was to propose a conservative treatment, namely concurrent radio chemotherapy after induction chemotherapy made of the TPF protocol. The evaluation after 03 cycles of the protocol shows an almost complete disappearance of the apparent tumor with a good tolerance profile. ***Conclusion***: Many analysis demonstrate a statistically significant reduction in locoregional recurrence amongst patients who received Induction chemotherpay despite that she has never provided an improvement to OS for OSCC patients. In the present case, chemotherapy with docetaxel, cisplatin and fluorouracil regimens is considered as an effective induction therapy for the treatment of locally advanced lip squamous carcinoma patients and should be suggested for better outcomes.

Keywords: Spectacular Response, Cisplatin Fluorouracil, locoregional.

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INTRODUCTION

Squamous cell carcinomas of the oral cavity (OSCC) is the 10th most common malignancy worldwide [1]. oral-mucosal squamous cell carcinoma (omSCC) is a substantially more aggressive disease that affects the oral mucosa, tongue, floor of mouth, and oropharynx, where it is estimated that between 18.6% and 44% of patients present with nodal disease depending on the subsite [2-5]. Lip SCC tends to present with early-stage disease and is most commonly seen in male patients over the age of 50 years. The UV radiation has been implicated as one of the strongest risk factors for development of lip SCC. Immunosuppression has been associated with an increased incidence, younger age of onset, and worse prognosis [6]. Other risk factors for lip SCC include tobacco and alcohol use, lower socioeconomic status, HPV, race, and genetic predisposition [7, 8]. Tumors with origin on the mucosal lip are staged concomitantly with the OSCC AJCC staging guidelines. As the lip is a site of anatomical overlap, primary squamous cell carcinoma of the lip (lip SCC) exhibits higher rates of nodal spread, mortality, and poor clinical outcome compared with cutaneous SCC [9-13]. However is it less aggressive compared with other OSCC [13-18].

Patients with metastasis SCC of the lip in cervical lymph nodes at the time of diagnosis, the 5-year survival rate of patients can reach only 30%, configuring a worse prognosis. The aggressive nature of advanced OSCC usually indicates a poor prognosis, requiring a multi-nodal treatment strategy of chemotherapy, surgery and radiotherapy. Despite advances in treatment options, locoregional recurrence (LRR) and distant metastasis (DM) rates remain high at around 30% and 25% respectively with minimal improvement to 5-year survival rates as they remain approximately at 50%. The patients with locally advanced stage of OSCC (stage III and IV) have been treated with multimodality therapy. For patients with locally advanced OSCC, rapid advancements regarding the choice of induction chemotherapy regimen have been made. There is substantial evidence related to the advantage and superiority of three-drug combination of Docetaxel, Cisplatin, and Fluorouracil (TPF) over the doublet regime of Cisplatin and Fluorouracil (PF) used previously as induction chemotherapy (ICT). We report the case of advanced lower lip squamous cell carcinoma in this case report treated with docetaxel, cisplatin and fluorouracil (TPF) as ICT with spectaculary response .

CASE REPORT

A 54 years Moroccan women old, with only a history of chronic asthma under treatment. The patient has been accusing, for more than a year, of a neglected painful tumefaction of the lower lip, evolving in a context of conservation of the general state. She consults the maxillofacial surgery department for care. She weighed 65 kilograms (Kgs) and he had a height of 158 cm. She was well oriented with regard to the date, time, place of his examination and she was cooperative. The clinical examination, from his head to his foot, finds a budding and ulcerous tumefaction of the lower lip (figure 1) and a biopsy of his lip lesion was scheduled under local anesthesia. Histopathology report poorly differentiated squamous cell carcinoma with foci of micro infiltrations, with positive staining for CK5/6 AND P63 on immunohistochemical study (figure 2). Blood Test Results Haemoglobin (Hb) -12gm, Total white blood cell (WBC) count- 17500/cu.mm, monocytes -5%, Granulocytes- 85%, Lymphocytes -12%, Esonophils-2%, Basophils - 0%, Total platelet count -2.88 cu.mm. Urea 12mg/dl, creatinine-0.8mg/dl, sodium132mmol/dl, potassium 4.5 mmol/L. The CRP determination returned to normal.

Fig-1: Patient with the initial presentation of budding and ulcerous tumefaction of the lower lip.

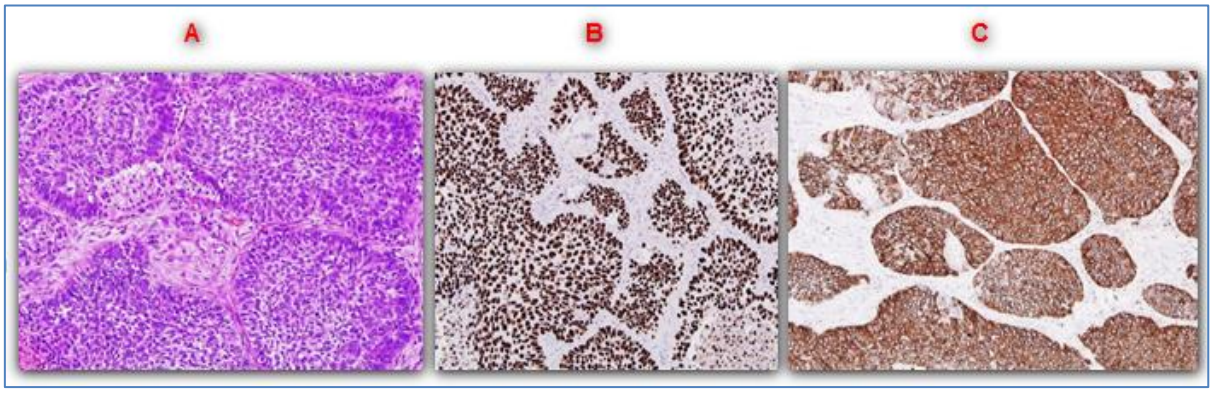

Fig-2: Morphological and immunohistochemical study in favor of a poorly differentiated squamous cell carcinoma (A= Mildly to moderately differentiated squamous cell carcinoma (HE, Gx400), B= Nuclear labeling positive for anti-p63, C= Positive membrane labeling with anti-CK5/6)

The cervico facial MRI shows a lesional process of the lower lip measuring 78x28X31mm. This process invades the dental roots with lysis of the mandibular cortex. The MRI also shows the presence of multiple submental and bilateral jugulo-carotidian adenopathies (figure 3). A remote extension assessment was carried out, including a FDG-PET scann, showing no other suspicious hypermetabolic foci on the rest of the structures explored from the head to mid-thigh (figure 4). The tumor was classified as cT4a N2c M0.

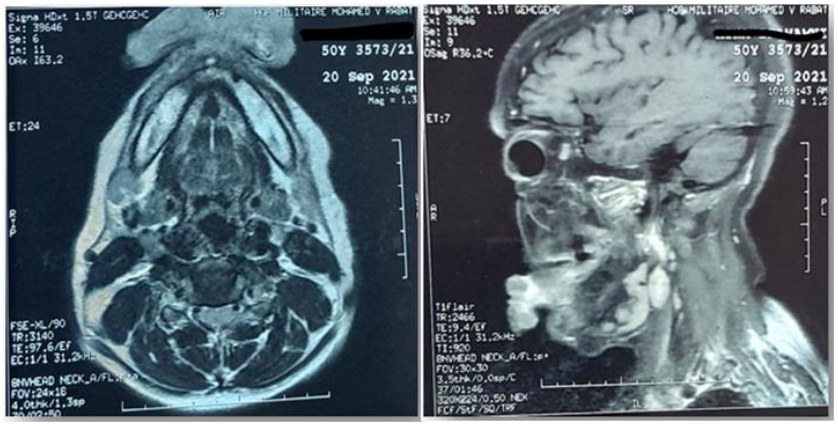

Fig-3: Transverse and sagittal sections of the cervico-facial MRI showing a locally advanced process of the lower lip

Fig-4: FDG-PET scan showing tumoral hypermetabolism of the lower lip with a max suv= 25 corresponding to the primary tumor known at this level

After a multidisciplinary discussion, and taking into account the mutilating nature of the surgery, which was refused by the patient, the decision was to propose a conservative treatment, namely concurrent radio chemotherapy after induction chemotherapy. We put the patient under the TPF protocol (docetaxel 75mg/m2, cisplatin 75mg/m2 and fluorouracil 1000mg/m2 continuous 24 hours infusion on days 1-4) every three weeks, plus the prescription of granulocyte growth factors for 5 days after each cure.

The evaluation after the first cure showed a clear clinical response with reduction in tumor size (figure 5). The evaluation after 03 cycles of the protocol shows an almost complete disappearance of the apparent tumor (figure 6) with a good tolerance profile. The cervico-facial computed tomography of control shows a reduction of the labial process measuring only 24mm of long axis, with reduction in number and size of the cervical adenopathies (figure 7). The patient is currently on concurrent chemoradiotherapy.

Fig-5: Clinical partial response after a single cycle of TPF chemotherapy

Fig-6: Spectaculary clinical response after three cycles of TPF induction chemotherapy

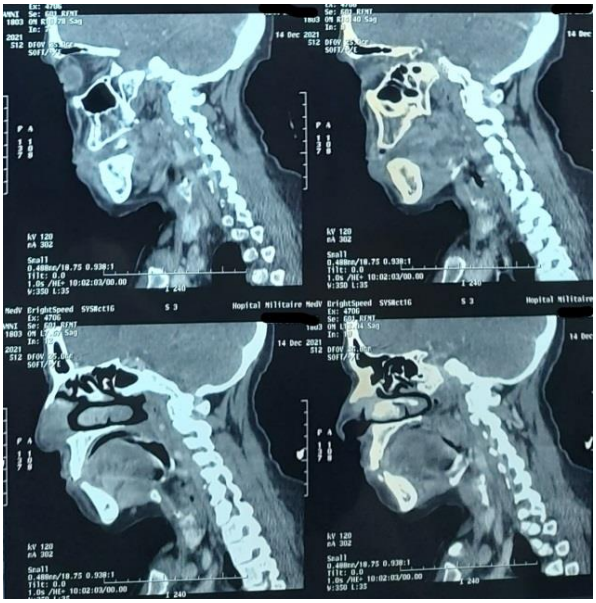

Fig-7: Cervico-facial computed tomography evaluation after three cycles of TPF induction chemotherapy showing a great reduction of the labial process measuring only 24mm of long axis

DISCUSSION

Cancers of oral cavity are grouped together with other cancers in the head and neck area. Survival rate is increased in oral cancer patients due to advanced medical technology. Survival rate of oral cancer patients can be improved with early identification and proper treatment, and with the help of adjuvant post-operative radiotherapy or chemo radiotherapy [5].

Given the variable outcomes of patients with lip SCC, several staging systems have been designed to help identify patients with a high risk of metastasis. The American Joint Committee on Cancer (AJCC) has developed separate staging guidelines for both cSCC and OSCC [19, 20]. Tumors with origin on the mucosal lip are staged concomitantly with the OSCC AJCC staging guidelines. Recommendations and modalities of imaging for lip SCC are continuously evolving. Imaging modalities include computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and positron emission tomography (PET). The role of imaging is multifaceted, and is directed at evaluating the extent of the primary tumor, nodal involvement and metastatic disease at presentation, and development of delayed nodal or metastatic disease. The MRI was found to have a higher sensitivity than CT—94% versus 83%, respectively [21].

Surgical excision for lip SCC is the first-line treatment unless contraindicated by patient comorbidity or refused by the patient. The head and neck NCCN guidelines recommend removal with approximately 1 to 2 cm of clinically tumor-free tissue [22]. There are no studies directly comparing excision with standard margins versus Mohs surgery for lip SCC.

Radiation therapy may also be considered as primary or definitive treatment in patients who are poor surgical candidates. A recent study of Australian patients with early-stage lip SCC showed a 90% 5- year recurrence-free survival with radiation alone [23].

The introduction of induction chemotherapy (ICT) showed promise for improving survival in advanced head and neck cancers from the high response rates to ICT demonstrated by trials in the 1990s [24,25]. It was hypothesized ICT would increase overall survival (OS), disease-free survival (DFS) and progression free survival by improving distant control [26]. Shrinking tumor volume prior to definitive treatment with ICT could enhance radiotherapy feasibility and tolerability whilst reducing the disfiguring effects of surgery and radiation [26]. Multiple randomized controlled trials (RCT) have evaluated OSCC response to ICT. Integration of data from independent studies is performed through meta-analysis where data from individual trials are pooled simultaneously to provide a summary for evidence-based care.

In our patient with locally advanced OSCC were given 3 cycles of induction chemotherapy with docetaxel cisplatin and fluorouracil regimens. After 3 cycles the CT scan was repeated to assess the clinical response. In previous study, author in their trial of docetaxel and cisplatin included 25 OSCC patients who received 5 treatment cycles ranging from 2 to 8 cycles, 8% patients showed complete and 25% showed partial response rate, with overall response rate as 33%. The toxicity was well tolerated and our patient did not discontinue her treatment due to side effect. In the clinical trials of phase I and II docetaxel plus cisplatin or fluorouracil (5-FU) for the treatment of locally advanced OSCC, showed prolonged survival and high clinical and pathological response rates (Colevas *et al*., 2000; Tubiana-Mathieu et al., 2000). In the clinical trials by Colevas *et al*. and Tubiana *et al*. of docetaxel with 5-FU showed over all response rates of 24-27% (Colevas *et al*., 2000; Tubiana-Mathieu *et al*., 2000). Whereas in the clinical trials of docetaxel with cisplatin, the overall response rates were reported as 33-76% and appeared to be more efficacious combination (Kienzer *et al*., 1998; Schoffski *et al*., 1999; Specht *et al*., 2000; Glisson *et al*., 2002). Another author evaluated the impact of induction chemotherapy with modified dose of docetaxel, cisplatin, plus 5-fluorouracil followed by concurrent chemotherapy in 52 OSCC patients of Asia and achieved partial response in 60% and complete response in 13.5% of the individuals after induction chemotherapy, moreover 42.3% had complete and 25 had partial response rates following radiotherapy and salvage surgery respectively. The most frequently observed adverse events in their study were neutropenia (35%), stomatitis (35%), anemia (25%), diarrhea (16%), and infections (13.5%) (Wang *et al*., 2017). In another research tolerability and effect of induction

chemotherapy with weekly docetaxel, cisplatin, and S-1 (weekly TPS) was evaluated which showed 80% had stage IV disease, while only 20% had stage III disease, among them 25.7% achieved complete response and 60% achieved partial response with overall Response Rate of Cisplatin Plus Docetaxel as Primary Treatment response rate as 86%.

Despite its perceived advantages, multiple meta-analyses did not find significant improvements to OS when ICT was added to treatment [27–32]. Meta-analyses by Zhang *et al*. [32] and Kim *et al*. [33] showed ICT using TPF did not improve OS for OSCC patients, with adverse events cited as a possible risk for increased morbidity and mortality [32,33]. However, interest in ICT has been renewed by the improved efficacy to survival using a taxane regimen, and improved loco-regional control by concomitant chemo-radiotherapy (CCRT) [30]. More studies are required to conclude whether TPF has a future role for increasing OSCC survival rates.

CONCLUSION

Many analysis demonstrate a statistically significant reduction in locoregional recurrence amongst patients who received ICT despite that she has never provided an improvement to OS for OSCC patients. In the present case, chemotherapy with docetaxel, cisplatin and fluorouracil regimens is considered as an effective induction therapy for the treatment of locally advanced lip squamous carcinoma and should be suggested for better outcomes.

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