

# Moving EGFR Targeted Therapy into the Induction Phase of the Management of Squamous Cell Carcinoma of the Head and Neck

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**Abstract:** Many advances in the treatment of squamous cell carcinoma of the head and neck have occurred in the past few years. Since the advent of cetuximab, a chimeric monoclonal antibody against epidermal growth factor receptor, the search for other efficacious targeted therapies has awakened the interest and curiosity of researchers and clinicians. Initially, cetuximab demonstrated effectiveness as single agent in heavily pretreated patients diagnosed with head and neck cancer, and has demonstrated to improve locoregional control and survival when combined with radiotherapy. The success of cetuximab has transitioned to other settings and with different modalities such as in combination with other conventional cytotoxic agents in the metastatic setting, combined with radiation therapy as part of concurrent treatment, and lately, in combination with other agents in the induction phase of the sequential approach. In this review, we discuss all different modalities in combination with cetuximab and how cetuximab has been incorporated into other clinical settings with only one goal in mind: improve the survival rates of our patients.

**Keywords:** Cetuximab, chemioimmunotherapy, concurrent chemoradiation, epidermal growth factor receptor, head and neck cancer, Human papilloma virus, induction therapy, organ preservation, radiation therapy, sequential approach.

## INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of all cancers and over 500,000 new cases are diagnosed yearly worldwide [1]. Approximately 49,260 new cases were diagnosed in the United States alone in 2010 [2, 3]. The overwhelming majority of head and neck cancers, over 90%, are squamous cell in origin [1]. Alcohol and tobacco use have been widely accepted as the most important risk factors, however, a newly recognized etiology is the presence of human papilloma virus (HPV) in these tumors [3]. The incidence of HPV positive cancers continues to rise both in total and as a proportion of all head and neck tumors. HPV positivity can be detected by either polymerase chain reaction (PCR) or by the presence of p16 immunohistochemistry (IHC) reactivity which demonstrates prior exposure to HPV in such tumors [4]. Several studies have shown that HPV positivity confers a good prognosis for SCCHN [5]. Nonetheless, all these reports are on the basis of retrospective studies. Its utility in terms of predicting response is unknown. The Radiation Therapy Oncology Group

ongoing RTOG1016 study is designed to evaluate patients whose tumors are HPV positive. The impact of this novel biomarker in terms of prediction of response to therapy is a matter of ongoing research [6].

Approximately two-thirds of patients present with advanced disease at diagnosis (stage III/IV), for which prognosis is poor [7]. Despite advances in the treatment of SCCHN, less than 30% of these cases will be cured and less than 50% will survive beyond 2 years [8]. Prognosis depends primarily on disease stage and performance status at the time of diagnosis [9,10]. If the disease is left untreated, median survival is approximately 4 months [10]. Treatment of locoregional advanced disease is quite complex. Careful patient selection and staging are key elements of achieving success. Various combined therapeutic modalities have been used, including concurrent chemoradiation (chemotherapy and radiation administered in a simultaneous manner), induction chemotherapy followed by irradiation (neoadjuvant chemotherapy followed by definitive radiation), and sequential therapy (induction chemotherapy followed by concurrent chemoradiation). Concurrent chemoradiation confers an absolute survival benefit of 8% at 2- and 5 years [11, 12]. When induction chemotherapy or sequential therapy is used, the most common therapeutic regimen is TPF [13].

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The development of biological therapies has expanded the treatment options in this disease. Among targeted agents, the monoclonal antibody against the epidermal growth factor receptor (EGFR), cetuximab, stands as a major accomplishment and addition to the treatment for SCCHN. The correlation between EGFR and carcinogenesis has been well established for over 30 years ago with studies that identified an overexpression of EGFR in approximately 90–100% of SCCHN specimens [14-16]. EGFR expression in tumors is associated with more aggressive disease, increased resistance to chemotherapy and radiotherapy, increased metastasis, poor prognosis, and decreased survival [17-19]. Cetuximab is approved in the United States for the treatment of refractory/metastatic SCCHN as a single agent, in combination with conventional chemotherapy as well, and in combination with radiation therapy for patients with locally advanced (LA)-SCCHN. Due to its efficacy and tolerability, several efforts have been made to move this agent to other therapeutic approaches (as part of sequential or induction regimens) as well as novel combined regimens. In this comprehensive review, the authors discuss the addition of cetuximab into the induction phase of the complex management of patients with LA-SCCHN.

### THE PLATFORM FOR INDUCTION CHEMOTHERAPY IN SCCHN

Induction chemotherapy has many theoretical advantages (i) reduction in tumor size which facilitates local therapy with surgery or radiation, (ii) treatment of micrometastatic disease, (iii) optimal delivery of chemotherapeutic drugs *via* undisrupted tumor vasculature, (iv) an opportunity to evaluate the biological activity of novel therapeutic agents, and (v) assess for potential predictive biomarkers. Moreover, induction chemotherapy offers the opportunity of assessing tumor response *in vivo* and thereby facilitating patient selection for subsequent organ-preserving interventions. We have witnessed this strategy being used, as organ-preserving therapy, for the larynx and hypopharynx [20-25]. These landmark studies have demonstrated that laryngeal preservation can be achieved in up to two-thirds of patients with stage III/IV laryngeal cancer without compromising overall survival (OS), when using induction chemotherapy followed by radiation. In addition, there is a decrease in the rate of distant metastatic recurrence in the patients treated with induction chemotherapy followed by radiation over the patients who underwent surgery followed by radiation.

Interestingly, concurrent chemoradiotherapy has shown to be superior than induction chemotherapy followed by radiation and to radiation alone in the RTOG91-11 trial [21].

Two large randomized phase III trials have demonstrated the benefits of induction chemotherapy in unresectable LA-SCCHN [26, 27]. The first of these two landmark studies, EORTC 24971/TAX 323, compared TPF versus cisplatin/fluorouracil (PF) chemotherapy regimen followed by definitive radiation. All patients had previously untreated and locoregionally advanced stage III/IV disease without metastasis. The TPF regimen consisted of docetaxel at a dose of 75 mg/m<sup>2</sup>, cisplatin at a dose of 75mg/m<sup>2</sup>, both at day 1, and fluorouracil 750 mg/m<sup>2</sup>/day continuous infusion for 5 days. The PF regimen consisted of cisplatin at a dose of 100 mg/m<sup>2</sup> and fluorouracil 1000 mg/m<sup>2</sup>/day continuous infusion for 5 days. Treatment was administered every 3 weeks for up to 4 cycles and was followed by radiotherapy within 4 to 7 weeks after completion of the last cycle of chemotherapy. A total of 358 patients were enrolled in this study, with 177 assigned to receive TPF and 181 assigned to receive PF. Most patients, 75.7% in the TPF group and 65.7% in the PF group, completed the chemotherapy as defined by protocol. Dose delays were more common in the PF group. Grade 3/4 neutropenia and leucopenia were more common in the TPF group, and severe thrombocytopenia and anemia were more common in the PF group. Deaths associated with toxic effects occurred in 4 patients in the TPF group (2.3%) and in 10 patients in the PF group (5.5%). Patients in the TPF group had a reduction of 27% in the risk of death, an improvement in median OS of 4.3 months, and an absolute increase in 3-year survival of 10.9% [26]. The second study, TAX 324, compared three cycles of TPF vs three cycles of PF; induction chemotherapy followed by 7 weeks of concurrent chemoradiotherapy (the sequential approach). The TPF regimen consisted of docetaxel 75 mg/m<sup>2</sup>, cisplatin 100 mg/m<sup>2</sup>, both at day 1, and fluorouracil 1000 mg/m<sup>2</sup>/day by continuous infusion for 4 days. The PF regimen consisted of cisplatin at a dose of 100mg/m<sup>2</sup> and fluorouracil 1000mg/m<sup>2</sup> continuous infusion for 5 days. Herein, concurrent chemoradiation was given within 3 to 8 weeks after the start of the third cycle of induction chemotherapy. Weekly carboplatin at an area under the curve (AUC) of 1.5 was administered for a maximum of seven doses. Radiation therapy consisted of 2 Gy/day, 5 days/week; for a total of 70 Gy. A total of 501 patients underwent randomization; 255 and 246

patients were assigned to the TPF and PF groups, respectively. At a median follow-up of 42 months, treatment with TPF resulted in a 30% reduction in the risk of death. Median survival was 71 months in the TPF group and 30 months in the PF group. Estimated 3-year survival was 62% in the TPF group and 48% in the PF group. As compared with the PF group, the TPF group had a significant reduction in the risk of disease progression or death. The median progression-free survival (PFS) was 36 months in the TPF group, and 13 months in the PF group. The overall response rate (ORR) after induction chemotherapy was 72% in the TPF group and 64% in the PF group. Grade 3 or 4 thrombocytopenia was more frequent in the PF group than in the TPF group (11% vs. 4%). Patients in the TPF group had fewer treatment delays than did those in the PF group (29% vs. 65%). No significant differences in the rates of adverse events were observed during chemoradiation [27].

These two studies established a novel regimen for induction therapy by adding docetaxel, a microtubule inhibitor, to the standard Cisplatin/Fluorouracil regimen. Most notably, these studies also proved the feasibility of delivering a triplet cytotoxic chemotherapy regimen without decreasing the number of patients that will proceed to definitive radiation therapy.

Despite the tremendous objective response, tolerability, and outcomes found with induction TPF followed by definitive radiation therapy or concurrent chemoradiation, we have not been able to define the best therapeutic approach for LA-SCCHN. What is superior: induction chemotherapy followed by definitive radiation, induction chemotherapy followed by concurrent chemoradiation, or induction chemotherapy followed by surgery and then concurrent chemoradiation? Thus far, only one randomized phase III study comparing both modalities of treatment has been completed. In this study, 382 patients with LA-SCCHN were randomized and treated with induction chemotherapy followed by concurrent chemoradiation or surgery. Induction chemotherapy had two arms: arm A received cisplatin 100 mg/m<sup>2</sup> on day 1 and 5-FU 1000 mg/m<sup>2</sup>/day by continuous infusion on days 1-5 every 21 days for 3 cycles; arm B regimen consisted of paclitaxel 175 mg/m<sup>2</sup> on day 1, cisplatin 100 mg/m<sup>2</sup> on day 2, and 5-FU 500 mg/m<sup>2</sup>/day by continuous infusion on days 2-6 every 21 days for 3 cycles. After completion of induction chemotherapy, patients underwent examination of tumor response by computer tomography imaging and ears, nose and throat specialists. If patients had a CR or PR greater than

80% in the primary tumor and no progression in the neck lymph nodes, the patient underwent chemoradiation. Patient with PR of less than 80% or stable disease in neck lymph nodes underwent surgical neck dissection followed by concurrent chemoradiation. Concurrent chemoradiation consisted of cisplatin 100 mg/m<sup>2</sup> on days 1, 22, and 43 plus radiation therapy to the primary tumor and to the clinically positive lymph nodes at a total dose of 70 Gy over a 7 week time span. The percentage of delayed cycles was significantly higher in arm A than in arm B (27% vs. 12%, respectively). A total of 12 patients discontinued induction chemotherapy due to toxicity (8 patients in arm A and 4 patients in arm B). Additionally, there were 12 toxic deaths (8 in arm A and 4 in arm B). The toxicity profile for the two treatment arms was similar, but mucositis was significantly worse in patients receiving the PF regimen compared with patients receiving the triplet regimen. Paclitaxel/PF treatment significantly improved CR when compared to PF alone. CR rates were 14% in the arm A compared to 33% in arm B. Organ preservation was achieved in 52% of the patients in arm A and 63% in arm B. The authors concluded that induction chemotherapy with Paclitaxel/PF was superior to PF [13].

#### **THE EFFECTIVENESS OF CHEMOIMMUNOTHERAPY IN SCCHN**

Cetuximab is a recombinant chimeric monoclonal antibody that binds to the extracellular ligand-binding domain of the EGFR and also the mutant receptor EGFRvIII, inducing internalization and downregulation of the EGFR [28,29]. This binding blocks the activation of the EGFR pathway, providing many antitumor effects such as induction of apoptosis, cell-cycle arrest at the G0/G1 boundary, inhibition of angiogenesis, decrease in metastasis, and enhancement of the sensitivity to radiotherapy [17, 30, 31]. Cetuximab is administered intravenously at a recommended loading dose of 400 mg/m<sup>2</sup> on day one followed by a weekly dose of 250 mg/m<sup>2</sup> [32-34]. The most serious side effects are dermatologic toxicity, infusion reactions and pulmonary toxicity [32].

The integration of cetuximab to radiation has had a significant impact in patients with locoregional advanced stage III/IV SCCHN [30,31]. The addition of cetuximab to radiation provides an absolute OS benefit of 9% at 5 years [31]. Given these encouraging results as well as safety and tolerability of cetuximab, further studies evaluated this agent in combination with chemotherapy as first line treatment for recurrent or

metastatic patients. Baselga *et al.* conducted a phase II study comparing the addition of cetuximab to platinum-based chemotherapy in platinum-refractory metastatic or recurrent SCCHN. All patients received a minimum of two and a maximum of four cycles of platinum-based chemotherapy alone or in combination with other agents before study entry. Ninety-six patients were enrolled to receive cetuximab 400 mg/m<sup>2</sup> loading dose on day one, with subsequent weekly doses of 250 mg/m<sup>2</sup> followed by cisplatin 60 mg/m<sup>2</sup> or carboplatin 250 mg/m<sup>2</sup>. For most of the patients (78%), the relative dose intensity (RDI) of cetuximab was > 90%. Less than 15% of patients experienced grade 3 or 4 toxicity, with acne-like skin reactions being the most common adverse effect. No cetuximab related-deaths were reported. ORR was 10%, with the median response lasting more than 5 months, and an OS of 183 days. In this study, the addition of cetuximab demonstrated good clinical activity with tolerable safety profile [36]. In a phase III study by Burtness *et al.*, 117 patients were randomized to receive either cetuximab plus cisplatin or cisplatin alone as first-line treatment in patients with metastatic or recurrent SCCHN. The patients received cetuximab 400 mg/m<sup>2</sup> on day one followed by weekly doses of 250 mg/m<sup>2</sup> plus cisplatin 100 mg/m<sup>2</sup> every 4 weeks or single-agent cisplatin 100 mg/m<sup>2</sup> every 4 weeks. The combination of cetuximab plus cisplatin demonstrated a higher ORR of 26% compared to 10% for cisplatin alone. However, OS and PFS were not statistically significant. The most common adverse reactions were neutropenia and skin toxicity, with no deaths related to cetuximab [37]. Another study conducted by Herbst *et al.* confirmed the superiority in terms of response rate when cetuximab was added to conventional platinum-based chemotherapy in resistant recurrent or metastatic SCCHN patients [38]. This study evaluated cetuximab plus cisplatin in patients with stable disease (SD) and progressive disease (PD1) after two 3-week cycles on cisplatin plus paclitaxel or cisplatin plus fluorouracil. Those patients who did not progress after two 3-week cycles continued their current therapy until progression of disease (PD2) and at that time they started cetuximab therapy. Cetuximab was administered at a loading dose of 400 mg/m<sup>2</sup> followed by weekly doses of 250 mg/m<sup>2</sup> plus cisplatin 75 or 100 mg/m<sup>2</sup> on day one every 3 weeks. The ORR was 18% for the SD group, 20% and 6% for the PD1 and PD2 group. The median duration of response was 4.2, 4.1, and 7.4 months for the PD1, PD2, and SD groups, respectively. Noteworthy, median OS for the SD patients was 11.7 months [38].

One of the most striking results using this monoclonal antibody in combination with chemotherapy

was found in the cetuximab (ErbituX) in combination with cisplatin or carboplatin and 5-fluorouracil in the first line Treatment of subjects with REcurrent and/or MEtastatic SCCHN (EXTREME) trial. This landmark study was the first randomized, placebo-controlled study to demonstrate a survival benefit in adding cetuximab to first line chemotherapy for recurrent or metastatic SCCHN patients. This study randomized 442 patients to receive either cisplatin or carboplatin plus 5-fluorouracil alone or in combination with cetuximab. All patients had confirmed recurrent or metastatic SCCHN and a Karnofsky performance score of 70 or more. The regimen consisted in cisplatin 100 mg/m<sup>2</sup> or carboplatin at AUC 5 as a one-hour intravenous infusion on day 1 and 5-fluorouracil 1000 mg/m<sup>2</sup> for 4 days by continuous infusion every 3 weeks. Cetuximab was given at its standard loading and weekly dosing. Patients received a maximum of six cycles of chemotherapy, and those in the cetuximab group who had at least SD received cetuximab monotherapy until disease progression or unacceptable toxic effects. Patients in both groups received similar number of chemotherapy cycles and over 83% of the patients had a RDI of 80% or more for each therapy agent. The frequency of toxicity events did not differ between the two groups. The OS was 10.1 months for patients treated with cetuximab plus chemotherapy and 7.4 months for chemotherapy alone. Therefore, an extension of 2.7 months in the median OS and a 20% reduction in the relative risk of death was associated with the addition of cetuximab to standard chemotherapy. [39]. Furthermore, a subset analysis of the EXTREME trial assessed the impact of treatment on the quality of life of the patients. The results showed that adding cetuximab to platinum-fluorouracil regimen does not negatively affect the quality of life of patients with recurrent or metastatic SCCHN [40]. A retrospective analysis has also evaluated the influence of *EGFR* gene copy number, determined by FISH, on clinical outcome in the EXTREME trial. There was no association between FISH score and OS, PFS, or best overall response. Patients with FISH positive tumors were evenly distributed between the chemotherapy plus cetuximab (50/158) and the chemotherapy alone (51/154) arms. With this data, we can conclude that *EGFR* gene copy number, as determined by FISH, is not a predictive biomarker for cetuximab efficacy in recurrent or metastatic SCCHN [41].

Substantial evidence supports the efficacy of cetuximab in combination with standard cytotoxic chemotherapy in recurrent and/or metastatic disease.

But, is it advantageous to add cetuximab to standard induction chemotherapy?

## **ADDING CETUXIMAB INTO INDUCTION CHEMOTHERAPY STRATEGIES**

### **As a Single Approach in Induction Therapy**

Cetuximab has been used as a single agent induction therapy followed by concurrent chemoradiation therapy. This has been evaluated in a phase II study that enrolled 29 patients. All the patients received induction cetuximab at its standard loading and weekly dosing for 4 weeks [42]. Potentially operable patients then received cetuximab 250 mg/m<sup>2</sup>, paclitaxel 40 mg/m<sup>2</sup>, and carboplatin at AUC =1 weekly for 5 weeks plus radiation 45Gy. Patients subsequently underwent endoscopic biopsy. If biopsy proven to be negative, the patients were further treated with 3 additional weekly doses of cetuximab, paclitaxel, and carboplatin plus radiation 22-27 Gy. Inoperable patients received 8 weeks of cetuximab, paclitaxel, and carboplatin plus radiation 66.6-72 Gy. All patients then received maintenance cetuximab 250 mg/m<sup>2</sup> weekly for 24 weeks. Responses to induction cetuximab using the RECIST criteria were 14 (61%) patients with SD, 7 (30%) had a PR, and 1 (4%) had a CR [42].

### **A Triplet Approach as Induction Therapy**

Kies *et al.* treated 47 patients with paclitaxel, carboplatin, and cetuximab induction chemotherapy. All patients had previously untreated stage IVA/B SCCHN. On week one, the patients received a combination of paclitaxel 135 mg/m<sup>2</sup>, carboplatin at AUC=2, and cetuximab 400 mg/m<sup>2</sup> loading dose followed by paclitaxel 135 mg/m<sup>2</sup>, carboplatin AUC=2, and cetuximab 250 mg/m<sup>2</sup> weekly for up to 6 weeks. Induction chemotherapy was followed by either surgery (n=1), radiation (n=23) or concurrent chemoradiation (n=23). Radiation or concurrent chemoradiation was started 2 to 3 weeks after completion of the induction chemotherapy phase. The patients received a total radiation dose of 66-72 Gy with concurrent cisplatin 100 mg/m<sup>2</sup> on days 1 and 22, for a total of 6 weeks. OS at 3 years was 91% with a PFS of 87%. Distant metastases were observed in 4 of 47 patients. Functional outcomes were encouraging, with a 3% gastrostomy tube dependence and 8% aspiration rate [43].

Wanebo *et al.* treated 74 stage III/IV SCCHN patients with induction chemotherapy using weekly cetuximab 250 mg/m<sup>2</sup>, paclitaxel 90 mg/m<sup>2</sup>, and

carboplatin at AUC=2. If there was a clinical response, patients underwent primary site biopsy at week 8. Patients with persistent tumor after biopsy at week 8 were treated with cetuximab 250 mg/m<sup>2</sup>, paclitaxel 30 mg/m<sup>2</sup>, and carboplatin at AUC=1 plus concurrent radiation for a dose of 50 Gy and primary site biopsy was repeated at week 14. If biopsy at week 8 did not reveal persistent tumor, patients received radiation (68-72Gy) plus weekly cetuximab 250 mg/m<sup>2</sup>, paclitaxel 90 mg/m<sup>2</sup>, and carboplatin AUC=2. Patients underwent salvage surgery if biopsy at week 14 revealed persistent tumor. A total of 40 patients underwent biopsy at week 8; no residual tumor was detected in 26(65%) patients, and 100% of patients achieved a CR after induction chemotherapy followed by concurrent chemoradiotherapy [44].

Tsoutsou *et al.* treated 13 LA-SCCHN patients with docetaxel, cisplatin, and cetuximab induction chemotherapy followed by concurrent chemoradiotherapy. The patients received docetaxel 40 mg/m<sup>2</sup>, cisplatin 60 mg/m<sup>2</sup> and cetuximab every 2 weeks for 2 cycles. Cetuximab was administered at the standard dose of 400 mg/m<sup>2</sup> on day one, and 250 mg/m<sup>2</sup> for subsequent doses. Induction chemotherapy was followed by concurrent chemoradiation with cisplatin 40 mg/m<sup>2</sup> and cetuximab 250 mg/m<sup>2</sup> weekly. Induction chemotherapy was well tolerated with only 1 patient experiencing grade 3 leucopenia and another patient experiencing grade 3 anemia. Only 1 patient had grade 3 mucositis secondary to chemoradiation. A total of 11 patients attained a CR. PFS, distant-free metastasis, and OS were 9.0, 9.53, and 9.61 months, respectively [45]. A similar triplet as an induction therapy was evaluated by Argiris *et al.* A total of 39 previously untreated stage III/IV SCCHN patients were treated with docetaxel 75 mg/m<sup>2</sup> on day 1, cisplatin 75 mg/m<sup>2</sup> on day 1, and cetuximab 250 mg/m<sup>2</sup> weekly. The first cycle included loading dose of cetuximab 400mg/m<sup>2</sup>. The cycles were repeated every 21 days for 3 cycles. Subsequently, patients received 70 Gy radiation with concurrent cisplatin 30 mg/m<sup>2</sup> and cetuximab 250 mg/m<sup>2</sup> weekly, followed by maintenance cetuximab 250 mg/m<sup>2</sup> weekly for 6 months. A total of 36 patients were able to receive all 3 cycles of induction chemotherapy. The ORR to induction chemotherapy was 86% with 73% CR. After concurrent chemoradiation, ORR was 100% with 86% CR. Serious toxicities during induction chemotherapy included grade 3/4 neutropenia and thrombocytopenia in 9 patients and grade 3 skin rash in 1 patient. Toxicities during concurrent chemoradiation included grade 3 mucositis in 15 patients [46].

## A Quadruplet Approach as Induction Therapy

A phase I study which was designed to determine the maximum tolerated dose (MTD) of 5-fluorouracil, in the TPF regimen, plus cetuximab induction chemotherapy followed by concurrent chemoradiation in LA-SCCHN patients reported a safe toxicity profile as a preliminary result [47]. The dose escalation scheme of 5-fluorouracil was 3 cohorts of 700, 850 and 1000 mg/m<sup>2</sup>/day by continuous infusion for 4 days. If there was no dose limiting toxicity (DLT), the dose of 5-fluorouracil was escalated to the next level. The regimen consisted of cetuximab 400 mg/m<sup>2</sup> on day one, followed by cetuximab 250 mg/m<sup>2</sup> weekly, plus TPF cisplatin 100 mg/m<sup>2</sup> and docetaxel 75 mg/m<sup>2</sup> every 21 days, for over 9 weeks. Subsequently, all patients received concurrent chemoradiation. A total of 30 patients were enrolled and 28 were assessable. The median age was 57 years, 92% had stage 4 disease, 71% were oropharynx, and all patients had a performance status of 0. No dose-limiting toxicity (DLT) was encountered on dose levels 1 and 2. At dose level 3 of 1,000 mg/m<sup>2</sup>, one DLT was encountered and 3 more patients were enrolled with no DLTs. In the expansion cohort at the MTD, three DLTs were encountered. The decision was made to decrease the 5-fluorouracil from 1,000 mg/m<sup>2</sup> to dose level 2 of 850 mg/m<sup>2</sup>. A total of 13 patients were enrolled at the MTD of 850 mg/m<sup>2</sup>. Cetuximab was delivered for an average of 7 weeks. The authors concluded that this quadruplet regimen appeared to be a safe and feasible combination. By decreasing 5-fluorouracil dosing to 850 mg/m<sup>2</sup>, the major toxicity of this regimen which is gastrointestinal (e.g., mucositis, enteritis, and diarrhea) was reduced. Moreover, C-TPF induces an ORR of 100% (6 PR and 22 CR) during the induction phase prior to concurrent chemoradiation [47].

Adkins *et al.* treated 30 patients with locoregionally advanced SCCHN with induction chemotherapy with weekly nab-paclitaxel 100 mg/m<sup>2</sup> and cetuximab 250 mg/m<sup>2</sup> with every 3 week cisplatin 75 mg/m<sup>2</sup> and 5-fluorouracil 750 mg/m<sup>2</sup>/day continuous infusion for 3 days. The patients were evaluated for clinical CR and PR at the primary tumor site after 2 cycles. Patients achieved a CR and PR of 53% and 47%, respectively. A total of 8 patients experienced grade 3-4 adverse events: infusion reaction to cetuximab (1), neutropenia/pneumonia (1), calf deep vein thrombosis (1), mucositis (1), rectal abscess (1), and asymptomatic neutropenia (3). In general, the regimen had an acceptable toxicity profile [48, 49].

A retrospective study analyzed the efficacy and tolerability in 23 patients who received cetuximab, docetaxel, cisplatin and 5-fluorouracil as induction chemotherapy for LA-SCCHN [50]. The course of therapy included cetuximab 400 mg/m<sup>2</sup> on day one followed by weekly cetuximab at 250 mg/m<sup>2</sup> plus docetaxel 75 mg/m<sup>2</sup>, cisplatin 75 mg/m<sup>2</sup>, and 5-fluorouracil 750 mg/m<sup>2</sup>/day infusion for 3 days being given every 3 weeks. This study showed a tumor response rate at the primary site of 71% as well as no grade 3/4 toxicity.

## CONCLUSIONS

LA-SCCHN is a disease that truly poses a challenge towards physicians. With perhaps a small window of opportunity for cure, clinicians face the difficult decision of providing the best treatment option tailored towards those patients. The two options that head and neck multidisciplinary group faces are: immediate and definitive concurrent chemoradiation versus induction chemotherapy followed by definitive concurrent chemoradiation (sequential approach). Effective management of patients with advanced SCCHN consists of a true multidisciplinary approach involving medical oncologists, head and neck surgeons, radiation therapists, speech therapists, nutritionists, pain service, and social workers.

Over the past two decades, we have witnessed the pendulum for and against induction chemotherapy sway several times for the management of SCCHN. Now, with the emergence of novel targeted agents such as cetuximab and the addition of taxanes to cisplatin/5-fluorouracil-based regimen, the door has been opened to revisit the idea of induction "chemoimmunotherapy" for SCCHN. Cetuximab has demonstrated, although in small studies, to be a safe and an effective agent in combination with chemotherapy for SCCHN in the induction phase. Superior response rates including CR were achieved with cetuximab plus induction chemotherapy than those reported in large randomized controlled trials, 68-72%, using TPF induction chemotherapy [27, 28]. Certainly, we need to define the best combination (agents and dosing schedule) to be paired with cetuximab: a triplet or quadruplet. Then, a large randomized phase III trial, with strict and rigorous eligibility criteria and trial design, will be required to finally answer the questions: Is induction therapy followed by concurrent chemoradiation superior than chemoradiation alone?, and Is there a subset of these patients who may have a greater benefit from this approach?

There is no question that targeted agents are offering the chance to attack malignant cells from different pathways, adding efficacy to the already established regimens and with better toxicity profile. Thus, it is in our hands to exploit this opportunity and change the dismal outcomes that we have seen in LA-SCCHN.

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