

Treatment of Locally Recurrent and Metastatic Squamous Cell Carcinoma of Head and Neck

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Abstract

The survival rate at 3 years after potentially curative surgical or radiation treatment for locally advanced squamous cell carcinoma of head and neck (SCCHN) remains quite poor at 30 to 50%. Over 50% of these patients relapse locally or at distant sites and with a median survival of 6-9 months. This review focuses on the established and experimental strategies seeking to improve this outcome. Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody engineered specifically to compete with the natural ligand for EGFR binding sites on the external surface of the cell membrane. This antibody have demonstrated significant disease control rate of over 45% as single agent in the locally recurrent/metastatic disease setting. The combination of cetuximab with platinum-based and taxane-based chemotherapy regimens has resulted in disease control rate of up to 80%. Studies are currently ongoing to assess the activity of immunotherapeutic agents like CTLA-4, PD-1, and PD-L1 inhibitors in the treatment of advanced SCCHN both in biomarker selected and unselected patient population with encouraging preliminary results. Moreover, the combination of these agents with standard chemotherapy regimens, and with cetuximab in the treatment of SCCHN is also being explored.

Keywords: Squamous cell carcinoma; Targeted therapies

Introduction

The annual incidence of Squamous Cell Carcinoma of Head and Neck (SCCHN) is approximately 60,000 cases in the United States and an estimated 12,290 deaths will occur in 2015. The vast majority of patients with oral cavity and pharynx cancer are diagnosed with advanced disease, including 47% of patients diagnosed with locally advanced disease (III, IVA, and IVB), and 18% of patients with metastatic disease (IVC) [1]. After initial therapy with surgery and radiation therapy, the 3-year survival is only 30 to 50% for patients with locally advanced disease [2]. However, greater than 50% of these patients relapse locally or at distant sites [3], and the median overall survival is only 6-9 months [4] and a disappointing 4 months for those whose disease has become platinum-

refractory [5]. In the recurrent or metastatic disease setting, the choice of chemotherapy is dictated mainly by whether or not the patient is chemotherapy naïve, and type of previous chemotherapy received in the first line setting. Over the last several years several single and combination regimens have been used in the locally recurrent/unresectable and metastatic disease setting with variable results. The median overall survival remains less than 1 year despite treatment with these single and combination agents [6]. The results from oral tyrosine kinase inhibitors have not been impressive [7]. This review will focus on established and promising emerging therapeutic strategies in the first line setting for the treatment of patients with locally recurrent/unresectable and metastatic SCCHN.

Targeted Therapies

Epidermal Growth Factor Receptor (EGFR) overexpression is observed in over 90% of SCCHN [8,9] and the levels of EGFR expression seem to correlate with poor prognosis and reduced survival [10,11]. This observation makes this transmembrane tyrosine kinase growth factor receptor an attractive target for therapeutic strategies to improve clinical outcome.

Cetuximab

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody designed specifically to compete with ligand for EGFR binding sites on the external surface of the cell membrane. Binding of cetuximab to EGFR prevents activation of tyrosine kinase within cells, resulting in apoptosis [12]. Cetuximab have demonstrated safety and efficacy when given as single agent for the treatment of patients with recurrent and/or metastatic SCCHN who progress on platinum-based therapy [13]. In a number of clinical studies, cetuximab has demonstrated meaningful clinical activity in the treatment of locally advanced, recurrent and/or metastatic SCCHN in the first-line setting in a number of studies [13-16].

In an open-label multicenter phase 2 study, 103 patients with disease progression following two to six cycles of platinum-based therapy received single-agent cetuximab (initial dose 400 mg/m² followed by subsequent weekly doses of 250 mg/m²) for 6 or more weeks (single-agent phase). Patients who experienced disease progression were allowed to receive salvage therapy with cetuximab plus platinum (combination-therapy phase). In the single-agent phase,

response rate was 13%, disease control rate (complete response/partial response/stable disease) was 46%, and median time to progression (TTP) was 70 days. The objective response rate was 0% during the combination-therapy phase, disease control rate was 26%, and TTP was 50 days. Median overall survival in the ITT population was 178 days [17]. The treatment was well tolerated. The most common cetuximab related adverse events were mild or moderate infusion reactions, asthenia, and grade 1 or 2 skin reactions such as acne-like rash, dry skin, and nail disorder. Most skin rashes were grade 1 or 2. Contrary to the finding in other SCCHN studies [14,17], this study found no association between skin rash and efficacy of cetuximab. The result of this study led to the FDA approval of cetuximab as single agent for the treatment of recurrent and/or metastatic SCCHN in March 2006.

Several chemotherapy agents have been combined with cetuximab in the salvage setting with no added benefit [14,18,19] (**Table 1**). Small molecule EGFR-TKIs have also been studied as single agents, and in combination with various chemotherapy regimens with no demonstrable improvement in outcome compared with cetuximab alone [20,21]. Therefore, cetuximab as a single agent remains the only targeted agent indicated in this population of patients.

Table 1 Cetuximab combined with chemotherapy in the treatment of recurrent/metastatic SCCHN. CDDP, cisplatin; PF, platinum (cis or carbo) + 5-fluorouracil; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

Author/Study	Regimen	ORR (%)	PFS (months)	OS (months)
Burtness et al [14]	CDDP+cetuximab	26	4.2	9.2
Bourhis et al [15]	PF+cetuximab	36	5.1	9.8
Buentzel et al [19]	Carbo/Taxol +cetuximab	56	5.0	8.0

Combination Chemotherapy

Platinum-based combination regimen

Platinum-based chemotherapy remains the bedrock of treatment for locally recurrent-inoperable and/or metastatic SCCHN. In the first line setting, the addition of cetuximab to cisplatin improved response rate over cisplatin alone [13]. Furthermore, the combination of cetuximab with cisplatin or carboplatin and fluorouracil showed significant benefit in phase 1/2 studies [14]. This led to the multicenter phase 3 study (EXTREME trial) where 442 patients with untreated recurrent and/or metastatic SCCHN were enrolled. Patients were randomized to receive cisplatin or carboplatin plus fluorouracil every 3 weeks for a maximum of 6 cycles versus the same chemotherapy plus cetuximab for a maximum of 6 cycles. Patients with stable disease, following a maximum of six cycles of chemotherapy plus cetuximab continued to receive cetuximab until disease progression or unacceptable

toxic effects [18]. The combination of chemotherapy plus cetuximab significantly prolonged overall survival compared with chemotherapy alone (median 10.1 versus 7.4 months, HR for death 0.80, 95% CI 0.64-0.99). There was also significant improvement in the progression-free survival (median 5.6 versus 3.3 months), and objective response rates (36% versus 20%). The most common grade 3 or 4 adverse events respectively in the chemotherapy-alone and cetuximab groups were anemia (19% and 13%, respectively), neutropenia (23% and 22%), and thrombocytopenia (11% in both groups). Sepsis occurred in 9 patients in the cetuximab group and in 1 patient in the chemotherapy-alone group (P=0.02). Of 219 patients who received cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions.

Based on the results of the EXTREME trial, the FDA approved cetuximab in combination with platinum-based therapy plus fluorouracil for the first-line treatment of patients with locally recurrent and/or metastatic SCCHN. Currently, single agent cetuximab is an acceptable treatment for cetuximab-naïve patients who have been previously treated with platinum-based chemotherapy. Cetuximab in combination with chemotherapy is also the standard first line treatment in patients with locally recurrent (inoperable) and/or metastatic SCCHN patients.

Taxanes

Cetuximab and taxane combinations have also shown promising activity in a number of studies in this population of patients. Hitt et al. enrolled 46 patients in a phase 2 study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. The overall response rate was 54% [95% Confidence Interval (CI) 39% to 69%], with 10 (22%) complete responses and a disease control rate of 80%. Median progression-free and overall survival times were 4.2 (95% CI 2.9-5.5 months) and 8.1 months (95% CI 6.6-9.6 months), respectively. Common grade 3/4 adverse events were acne-like rash (24%), asthenia (17%) and neutropenia (13%). While prior chemotherapy and the development of acne-like rash were associated with tumor response but not survival, there was no association between tumor EGFR expression, or EGFR gene copy number and outcome [22].

In the GORTEC 2008-3 trial [23], Guigay et al. enrolled 54 patients with previously untreated locally recurrent and/or metastatic SCCHN. Patients were treated with weekly cetuximab and four 3-week cycles of docetaxel 75 mg/m² and cisplatin 75 mg/m², followed by maintenance cetuximab until disease progression or unacceptable toxicity. The primary endpoint, which was overall response rate was 54%. The median PFS and OS were 7.1 months and 15.3 months, respectively. The result of the GORTEC study was comparable to outcome observed with combination of cisplatin, 5-FU, and cetuximab in the EXTREME trial [18].

In the second and third-line setting, Knoedler et al. treated 84 platinum-pretreated locally recurrent and/or metastatic SCCHN patients with weekly cetuximab and docetaxel 35

mg/m² (3 weeks out of 4) [24]. The observed partial response rate and disease control rate were 12% and 39%, respectively. The response rate was independent of previous platinum sensitivity.

Other Combination Chemotherapy Studies

There are ongoing studies evaluating cetuximab-based combination regimens in advanced SCCHN. CECAVI is a study of cetuximab in combination with chemotherapy for patients with SCCHN with the purpose of demonstrating the efficacy of cetuximab in combination with carboplatin and vinorelbine as second line treatment in patients with recurrent or metastatic SCCHN who have progressed during or after treatment with first line cisplatin [25].

ELAN-UNFIT is a Phase III Trial comparing methotrexate and cetuximab in first-line treatment of recurrent and/or metastatic SCCHN. This study is designed to test whether cetuximab improves efficacy/tolerance as compared to methotrexate in first line treatment of unfit patients, 70 years or older with recurrent and /or metastatic SCCHN. Efficacy will be assessed by failure free survival [25].

Immune checkpoint therapy

Pembrolizumab (MK-3475) is a humanized monoclonal antibody that blocks interaction of PD-1 with its ligands, PD-L1

and PD-L2, thereby promoting activity of tumor-specific effector T cells. Preliminary result of an expansion cohort of SCCHN patients enrolled in KEYNOTE-012 study was initially presented by Tanguy Seiwert at the 2015 ASCO annual meeting [26]. The study enrolled 132 patients with locally recurrent and/or metastatic SCCHN regardless of PD-L1 expression or HPV status to receive a fixed dose of 200 mg pembrolizumab, intravenously, once every 3 weeks. Data from 99 patients out of 132 treated patients were available for the preliminary efficacy analysis. The patient population consisted of those who completed a post-baseline scan or discontinued therapy prior to the scan due to clinical progression or AE. The ORR (confirmed and unconfirmed) by RECIST 1.1 was 18.2% (95% CI, 11.1-27.2) and 31.3% with stable disease.

Other ongoing immunotherapy-based trials for the treatment of advanced SCCHN include KEYNOTE-055, a phase 2 study of pembrolizumab in patients with locally advanced and/or metastatic SCCHN who have failed or relapsed following treatment with platinum-based and cetuximab-based treatments [25]. This study recently completed accrual and the result is awaited.

Another immune checkpoint inhibitor targeting PD-L1, durvalumab (MED14736) is being evaluated in combination with tremelimumab against standard of care in a phase III randomized, open-label, multi-center, global study for first-line treatment of recurrent or metastatic SCCHN patients [26] [(Table 2) for ongoing phases 2 and 3 immune checkpoint clinical trials].

Table 2 Ongoing Phases II and III immune checkpoint inhibitor clinical trials in locally recurrent/metastatic SCCHN.

Study title	Study Phase	Clinical Trial Identifier
Phase II Study of MEDI4736, Tremelimumab, and MEDI4736 in Combination w/ Tremelimumab Squamous Cell Carcinoma of the Head and Neck	2	NCT02319044
Phase II Study of MEDI4736 Monotherapy in Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck	2	NCT02207530
Study to Assess MEDI4736 With Either AZD9150 or AZD5069 in Relapsed Metastatic Squamous Cell Carcinoma of Head & Neck	2	NCT02499328
Pembrolizumab (MK-3475) Versus Standard Treatment for Recurrent or Metastatic Head and Neck Cancer (MK-3475-040/KEYNOTE-040)	3	NCT02252042
Study of MEDI4736 Monotherapy and in Combination With Tremelimumab Versus Standard of Care Therapy in Patients With Head and Neck Cancer	3	NCT02369874
A Study of Pembrolizumab (MK-3475) for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (MK-3475-048/KEYNOTE-048)	3	NCT02358031
Phase III Open Label First Line Therapy Study of MEDI 4736 With or Without Tremelimumab Versus Standard of Care (SOC) in SCCHN (KESTREL)	3	NCT02551159

Summary

Majority of patients with SCCHN are diagnosed with advanced disease, with 52% of patients diagnosed with locally advanced disease (III, IVA, and IVB) and 10% of patients with metastatic disease (IVC). After initial therapy with surgery and radiation therapy, the 3-year survival is only 30 to 50% for patients with locally advanced disease. However, greater than 50% of these patients relapse locally or at distant sites, and

with a median survival of 6 – 9 months. The survival in platinum-refractory disease remains dismal and is less than 4 months. The introduction of cetuximab as single agent, and later in combination with various chemotherapy regimens has led to improvement in survival. However, most of these cytotoxic agents are extremely toxic posing a challenge for patients older than 70 years of age and patients with poor performance status. Unfortunately, most patients with SCCHN are older than 65 years, and most have a performance status of ECOG 1 and greater.

Recently, the success of immunotherapeutic agents that target immune-checkpoint molecules like cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death- 1 (PD-1), and programmed cell death ligands (PD-L1 and PDL-2) in the treatment of cancer has been described. Currently, PD-1, PD-L1, and CTLA-4 inhibitors are being tried as single agents, and in combinations, in various clinical trials around the world with promising preliminary results. These agents seem to have a more tolerable toxicity profile.

The activity of immunotherapeutic agents seem to depend on the tumor microenvironment. High concentrations of tumor-specific CD8+ lymphocytes, NK cells, and tumor antigens seem to enhance the antitumor effects of these agents. This has stimulated the concept of an initial cytotoxic chemotherapy or radiation therapy followed by immunotherapy. Perhaps, the next generation of clinical trials on advanced SCCHN should focus on cytotoxic chemotherapy and immunotherapy in various combinations.

Disclosure

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References

- Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. *CA: a cancer journal for clinicians* 65: 5-29.
- Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winkquist E, et al. (2007) Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 357: 1705-1715.
- Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortés-Funes H, et al. (2005) Phase II multicenter study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *Journal of Clinical Oncology* 23: 5568-5577.
- Argiris A, Li Y, Forastiere A (2004) Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. *Cancer* 101: 2222-2229.
- Leon X, Hitt R, Constenla M, Rocca A, Stupp R, et al. (2005) A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy. *Clinical Oncology* 17: 418-424.
- Price KA, Cohen EE (2012) Current treatment options for metastatic head and neck cancer. *Current treatment options in oncology* 13: 35-46.
- Vermorken JB, Specenier P (2010) Optimal treatment for recurrent/metastatic head and neck cancer. *Annals of oncology* 21: 252-261.
- Hansen AR, Siu LL (2013) Epidermal growth factor receptor targeting in head and neck cancer: have we been just skimming the surface? *Journal of Clinical Oncology* 31: 1381-1383.
- Herbst RS, Langer CJ (2002) Epidermal growth factor receptors as a target for cancer treatment: the emerging role of IMC-C225 in the treatment of lung and head and neck cancers. *In Seminars in oncology* 29: 27-36.
- Nicholson RI, Gee JMW, Harper ME (2001) EGFR and cancer prognosis. *European journal of cancer* 37: 9-15.
- Ang KK, Berkey BA, Tu X, Zhang HZ, Katz R, et al. (2002) Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer research* 62: 7350-7356.
- Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, et al. (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *New England Journal of Medicine* 354: 567-578.
- Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, et al. (2007) Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *Journal of Clinical Oncology* 25: 2171-2177.
- Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA (2005) Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *Journal of Clinical Oncology* 23: 8646-8654.
- Bourhis J, Rivera F, Mesia R, Awada A, Geoffrois L, et al. (2006) Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *Journal of clinical oncology* 24: 2866-2872.
- Vermorken JB, Mesia R, Vega-Villegas ME, Remenar E, Hitt R, et al. (2006) Cetuximab in combination with cisplatin or carboplatin and 5-fluorouracil (5-FU) in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (RandM SCCHN)(EXTREME). *In ASCO annual meeting proceedings* 24: 5537.
- Herbst RS, Arquette M, Shin DM, Dicke K, Vokes EE, et al. (2005) Epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck: A phase II, multicenter study. *J Clin Oncol* 23: 5578-5587.
- Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecky A, et al. (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. *New England Journal of Medicine* 359: 1116-1127.
- Buentzel J, De Vries A, Micke O (2007) Experience with cetuximab plus paclitaxel/carboplatinum in primary platinum-resistant recurrent head and neck cancer. *In ASCO Annual Meeting Proceedings* 25: 6077.
- Shaib W, Kono S, Saba N (2012) Anti-epidermal growth factor receptor therapy in squamous cell carcinoma of the head and neck. *Journal of oncology*.
- Stewart JSW, Cohen EE, Licitra L, Van Herpen CM, Khorprasert C, et al. (2009) Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell

- carcinoma of the head and neck. *Journal of Clinical Oncology* 27: 1864-1871.
22. Hitt R, Irigoyen A, Cortes-Funes H, Grau JJ, Garcia-Saenz JA, et al. (2012) Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Annals of Oncology*, 23: 1016-1022.
 23. Guigay J, Fayette J, Dillies AF, Sire C, Kerger JN, et al. (2012) Cetuximab, docetaxel, and cisplatin (TPEX) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase II trial GORTEC 2008-03. In *ASCO Annual Meeting Proceedings* 30: 5505.
 24. Knoedler MK, Gauler T, Matzdorff A, Jordan O, Schroeder M, et al. (2009) Multicenter phase II study of cetuximab plus docetaxel in 84 patients with recurrent or metastatic, platinum-pretreated SCCHN. In *ASCO Annual Meeting Proceedings* 27: 6048.
 25. ClinicalTrials.gov. Accessed on 12/24/2015.
 26. Seiwert TY, Haddad RI, Gupta S, Mehra R, Tahara M, et al. (2015) Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): preliminary results from KEYNOTE-012 expansion cohort. In *ASCO Annual Meeting Proceedings* 33: LBA6008.