

Case Report

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Prolonged Survival with Anti-EGFR Therapy in Head and Neck Squamous Cell Carcinoma - A Case Series

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Abstract

Head and Neck Cancer (HNC) is the sixth most common cancer worldwide, with about 650,000 patients newly diagnosed annually. In the late 1990s, surgery followed by postoperative Radiotherapy (RT) or RT alone was the standard therapeutic modality for loco regionally advanced HNSCC (LA-HNSCC). Since chemotherapeutic agents were identified to have additional effects when combined with RT, Chemo-Radiotherapy (CRT) has become the standard treatment over the last decade for patients with LA-HNSCC who were not candidates for surgery. Despite the heterogeneity of both tumor location and genetic aberrations, 90% of HNCs are Histologically Squamous Cell Carcinomas (HNSCCs). Hereby we present a case series of patients with HNSCC who were benefited with Anti-EGFR therapy with a prolonged survival.

Introduction

Head and Neck Cancer (HNC) is the sixth most common cancer worldwide, with about 650,000 patients newly diagnosed annually [1]. In the late 1990s, surgery followed by postoperative Radiotherapy (RT) or RT alone was the standard therapeutic modality for loco regionally advanced HNSCC (LA-HNSCC). Since chemotherapeutic agents were identified to have additional effects when combined with RT, Chemo-Radiotherapy (CRT) has become the standard treatment over the last decade for patients with LA-HNSCC who were not candidates for surgery. Clinical trials have demonstrated that concurrent CRT can improve Overall Survival (OS) compared with RT alone [2]. Despite the heterogeneity of both tumor location and genetic aberrations, 90% of HNCs are Histologically Squamous Cell Carcinomas (HNSCCs). At the time of diagnosis, most patients with HNSCC have loco regionally advanced disease which requires a multimodality therapy [3].

The Epidermal Growth Factor Receptor (EGFR) is expressed in about 80% of patients with HNSCC [4]. EGFR overexpression has been found to be an independent factor associated with unfavorable prognosis in these patients [5]. Anti-EGFR agents can block the EGFR, thereby inhibiting its downstream function. While radiation increases EGFR expression in cancer cells, blockade of EGFR signaling makes cancer cells more sensitive to radiation [6]. Since a randomized phase III trial demonstrated survival benefit from the combination of cetuximab and RT compared with RT alone [7]. Trials further evaluated other agents like Panitumumab,

other agents also in the concurrent setting. The good results in concurrent setting also led to trials evaluating the addition of targeted therapy along with chemotherapy and radiotherapy [8].

Case Report

Case 1

A 32 years old male patient who consumed moderate alcohol since last 10 year presented with chief complaints of pain in the left ear and minimal discharge with decreased hearing from left ear since 2 months. Biopsy-External auditory canal was suggestive of SCC. Whole Body PET CT scan showed Hyper metabolic active disease at the site of known primary (left external auditory canal). He Underwent Wide local excision of left external auditory canal mass with left extended Parotidectomy. On histopathological examination, all margins were free; Overall features were in favor of Recurrent/Residual SCC left external ear pT2N0M0. On IHC, tumor cells were CK + 5/6, p63 +, EMA +; CEA-polyclonal -Focal positive. He Underwent Radiation Therapy to a dose of PTV 45:4500cGy in 25 fractions + PTV 60: 6000cGy in 30 fractions. Follow up scans revealed a complete response until 36 months after the radiotherapy followed by progression with multiple lung mets, mediastinal lymph node Mets. CT Guided Right lung mass biopsy was s/o Squamous cell carcinoma. On this patient was started on carboplatin with paclitaxel for 6 cycles showing a stable disease. Following which patient was started on Gefitinib 250 mg as a maintenance regimen which had a very good response without

any progression till date with a PFS of 16 months.

Case 2

A 48 years old patient who was a known hypertensive since last 7 years on treatment with no history of any addictions came with the chief complaints of Ulcer over the left margin of tongue since 1 month. MRI Neck, Tongue was suggestive of Enhancing lesion in left lateral border with enlarge LN. HPE revealed Well differentiated SCC, left lateral border of tongue infiltrating muscle, Nodes: Negative, T2N0M0. He Underwent Wide Excision Glossectomy +with Left SOHD. On frozen section, all the borders were free of tumor cells. Post op 3 month's patient started complaining of pain in the left side of the face and ear though local examination was within normal limits. Pain started increasing over left side of face, submental region, experiencing difficulty in chewing. Whole body PET CT showed metabolically active large heterogeneously enhancing soft tissue seen involving the floor of the mouth, extending along the left tonsillo-lingual sulcus into the left tonsil fossa involving the left valecula and causing erosion of the left half of the hyoid bone and was suggestive of disease recurrence. Patient Received 3 cycles of chemotherapy with cetuximab + Abraxane + Carboplatin which showed a partial response on a follow up scan followed by EBRT by Image Guided Radiotherapy (IGRT) technique to head and neck followed by evidence of disease progression. He was then started with maintenance therapy on cituximab for 112 weeks with intermediate scans s/o near complete response and a stable disease till date making a PFS of 23 months.

Case 3

A 47 years old male patient with no known comorbidities and no addictions came with the complaints of difficulty in swallowing and change in the voice since last 2 months. On examination revealed edema in the left AE with Decreased movements of the left vocal cord. CT Neck revealed a mass in the left pyriform sinus and involving left AE fold and false cord. Enlarged lymph nodes in left upper mid and lower deep cervical regions. FNAC of neck nodes was positive for malignant cells. He Received CCRT to face and neck to a with Cisplatin. Whole Body PET CT revealed metabolically active residual disease in the left pyriform fossa. Metabolically active lymphadenopathy. He Received 3 cycles of chemotherapy with Paclitaxel & Cisplatin with Tab. Gefitinib 250mg. Whole Body PET CT showed No metabolically active residual/recurrent disease suggesting excellent response to chemotherapy.

After 5 years' patient recurred with Invasive moderately differentiated keratinizing squamous carcinoma with clear resection margins. He was started on mitoxan and carboplatin followed by EBRT by 3DCRT technique to head and neck with concurrent cisplatin. 2 months' post CCRT, MRI Neck with Contrast reveals post-operative changes with homogenously enhancing mass involving the right half of tongue, crossing the midline towards left

side and contiguously infiltrating the floor of mouth with involvement of the body of mandible anteriorly. MRI brain was normal. After this the patient was started on gemcitabine and carboplatin which gave a complete response. After 8 cycles of chemotherapy, MRI Neck reveals disease recurrence. Then patient was started on gefitinib 250mg OD achieving partial response with a stable disease on interval scans till date making a PFS of 22 months.

Discussion

Activation of the proto-oncogene EGFR is an early event in head and neck carcinogenesis. EGFR mRNA is highly expressed in SCCHN and contributes to the pathogenesis of this disease [9]. High levels of EGFR protein expression, as detected by Immunohistochemistry (IHC) have been seen in up to 90% of SCCHN tumors and is associated with poor prognosis [10]. The loss of growth control in head and neck squamous cell carcinoma (HNSCC) is characterized by acquisition of an autocrine regulatory pathway involving the Epidermal Growth Factor Receptor (EGFR) [11]. The primary rationale for the design of EGFR targeting strategies has been based on the increased EGFR expression levels detected on tumor cells, although evidence suggests that constitutive EGFR activation can occur in the absence of increased expression [12]. In addition to the importance of EGFR expression in human HNSCC, many studies have reported anti-tumor effects when EGFR targeting strategies that were used in preclinical HNSCC models [13].

EGFR inhibitors have been shown to abrogate the growth of HNSCC cell lines and xenografts when administered alone, or in combination with standard therapy such as chemotherapy and/or radiation [14]. The EGFR monoclonal antibody cetuximab has been combined with cisplatin in platinum-refractory HNSCC patients in a phase III trial supported by the Eastern Cooperative Oncology Group (ECOG) that demonstrated enhanced response rates when subjects received the combined treatment regimen [15]. The FDA approved the use of cetuximab for SCCHN in 2006 based on the results of a phase III trial showing prolonged survival when cetuximab was administered in conjunction with radiation [16]. This was the first phase III trial to demonstrate a survival advantage using a molecular targeting agent combined with radiation. In addition, the combination of radiation and cetuximab did not significantly increase the toxicity profile or compromise the effective delivery of full course external beam radiation therapy. It is noteworthy that cetuximab was the first new drug approved for use in this cancer in 45 years. While the combination of cetuximab and radiation increased survival compared with radiation alone, cetuximab did not reduce the incidence of distant metastases nor did it completely prevent local-regional failure. These facts indicate the persistence of oncogenic signaling pathways.

Bonner, et al. reported improved loco regional disease control, progression-free survival, and overall survival with the addi-

tion of cetuximab to radiation in patients with locally advanced HNSCC [16]. Chemo radiation is currently considered optimal therapy for this group of patients [3]. However, concurrent chemotherapy is not only associated with additional adverse effects such as nausea, vomiting, and neutropenia, but also with severe oropharyngeal mucositis in more than 50% of patients. This latter adverse event represents a serious challenge to QOL, costs, and management in these patients. A large meta-analysis of individual patient data has also reported that concurrent chemotherapy is not associated with an improvement in overall survival in patients over the age of 70 years [4]. It is unclear whether this lack of efficacy is a result of one or some combination of reduced efficacy of treatment, increased mortality of treatment, and effects of competing risks. The addition of cetuximab to radiation was not associated with chemotherapy-specific toxicities or an increase in the frequency of severe mucositis beyond that seen with radiation alone [16]. The most common and significant effect was skin rash, which occurred in 87% of patients. The rash was severe in 17% of patients. Acute infusion reactions also occurred in 3% of patients. Overall QOL was neither improved nor diminished by the addition of cetuximab to radiation.

EGFR-specific tyrosine kinase inhibitors such as erlotinib have also been explored as antitumor agents in SCCHN, although phase III data are lacking [17]. Several ongoing US and international clinical trials are exploring the combination of chemo radiotherapy with EGFR targeting as a curative treatment strategy. Also, the response rates and survival times of patients who received gefitinib as first-line therapy were not significantly different to those of patients who had received prior chemotherapy. Overall, the median times to progression and death were 3.4 and 8.1 months, respectively, with an estimated 1-year survival of 29%. These results are more favorable than those achieved with chemotherapy in this setting, but with the additional benefit of reduced treatment-related toxicity. There was only a single case of grade 4 toxicity (hypercalcaemia), a 4-6% incidence of grade 3 toxicity (anorexia, diarrhoea, nausea and hypercalcaemia), grade 1 or 2 skin rash in 48% and grade 1 or 2 diarrhoea in 50% [18].

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| Cohen | II | Gefitinib 500 mg QD | R&M | RR 11%, med survival 8.1 mo, 1-year survival 30% |
| Kane | II | Gefitinib 250 mg QD | R&M | RR 1.4%, med survival 5.5 mo, 1-year survival 19% |

Other questions that remain to be answered include the timing of radiation or chemotherapy delivery with EGFR targeted therapies and the role of other targets, in addition to EGFR. There is no evidence to date of an association between Human Papilloma Virus (HPV) status of the tumor and response to EGFR targeting. An improved understanding of EGFR signaling interactions with other oncogenic pathways should facilitate the design of more ef-

fective targeting strategies by elucidating the critical proliferative and survival pathways that persist in the setting of EGFR blockade.

Conclusion

In conclusion, this case series demonstrates that the addition of an anti-EGFR agent to conventional RT or CRT does improve clinical outcomes compared with CRT in patients with HNSCC. These results indicate that anti-EGFR agents prolong the survival and clinical course of patients with HNSCC, though advanced studies on EGFR signaling interactions with other oncogenic pathways are required for better study of these agents and its clinical application.

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