JOURNAL OF CASE REPORTS 2016;6(3):313-316

Nimotuzumab in Combination with Chemoradiotherapy in a Case of Locally Advanced Oesophageal Malignancy

J B Sharma
Consultant Medical Oncologist, Action Cancer Hospital, A - 4, Paschim Vihar, New Delhi - 110063, India.

Abstract:

The cases of esophageal cancer are rapidly increasing worldwide and the highest rates found in Southern and Eastern Africa and Eastern Asia. The treatment option for esophageal cancer is either surgical or non-surgical. We report a 70 year old obese female without any concomitant disease diagnosed with locally advanced esophageal carcinoma with metastasis (T4N1M0). Patient was treated with concurrent chemoradiation along with nimotuzumab 200 mg. The chemotherapy was with cisplatin in the dose of 35 mg/m^2 weekly for a period of seven cycles and radiotherapy was with a total radiation dose of 59.5 Gy. The patient responded well to the combination therapy by showing a near absence of tumor lesion, which was evident on a repeat, post treatment whole body PET-CT Scan. Patient tolerated the therapy well without any significant adverse effects. Nimotuzumab was found effective with chemoradiotherapy in treatment of esophageal squamous cell carcinoma.

Key words: Oesophageal Neoplasms, Squamous Cell Carcinoma, Nimotuzumab, Cisplatin, Chemoradiotherapy.

Introduction

An estimated 482,300 new esophageal cancer cases and 406,800 deaths occurred in 2008 worldwide. Incidence rates vary internationally by nearly 16-fold, with the highest rates found in Southern and Eastern Africa and Eastern Asia [1]. Esophageal cancer encompasses two distinct histopathological groups: squamous cell carcinoma and adenocarcinoma but they are often managed as a single entity.

Squamous cell carcinoma accounts for approximately 40% of the esophageal malignancies, but there has been an increase in the incidence rates of adenocarcinomas in the western countries. Most of these patients are locally or regionally advanced or disseminated cancer at presentation, irrespective of histological type. The treatment for esophageal cancer is either surgical or non-surgical. Surgery is considered as the standard treatment for patients with resectable esophageal cancer however surgery alone or any other single modality is ineffective in most of the patients. In case of advanced esophageal squamous cell carcinoma (ESCC) systemic

Corresponding Author: Dr. JB Sharma
Email: drjbsharma7@gmail.com
Received: March 17, 2015 | **Accepted:** May 26, 2015 | **Published Online:** July 15, 2016

Conflict of interest: None declared | **Source of funding:** Nil | **DOI:** http://dx.doi.org/10.17659/01.2016.0077

chemotherapy is generally effective and it forms an important part of the multidisciplinary treatment approach along with radiotherapy [2]. In particular, cisplatin and fluorouracil (CF) combination therapy is an accepted line of therapy. Based on the positive results of RTOG -85-01 trial, conventional nonsurgical treatment line is chemoradiation but it is associated with higher incidence of toxicity. In an attempt to help improve the management of esophageal carcinoma, targeted therapies with lesser toxicities have been considered as new approach. In particular, targeting epidermal growth factor receptors might prove prudent because of its high levels of expression in carcinoma especially ESCCs [3].

Case Report

A 70 year old morbidly obese female patient (BMI = 43.5 kg/m^2) apparently without any concomitant disease presented with history of dysphagia, odynophagia (solids more than liquids) and nausea for a duration of 2 months. An upper gastrointestinal (UGI) endoscopy showed a oesophageal polypoidal lesion, 7 cms in length, extending 27 cms to 34 cms from incisors. Esophageal biopsy of the same showed moderately differentiated keratinized squamous cell carcinoma. Whole body PET-CT scan after injection of 10 m Ci of F8-18 FDG was done in this patient to know the extent and stage the tumor, to decide the treatment strategy. The scan revealed a malignant esophageal lesion with aortic and mediastinal lymph node metastases. Figure 1A, 2A and 3A depicts the esophageal lesion in 3 different views: fused axial, coronal and sagittal respectively showing esophageal wall thickening with increased FDG uptake and loss of fat planes and metastases to aortic and mediastinal lymph nodes. Based on the above investigations the patient was diagnosed of locally advanced esophageal carcinoma with metastasis (T4N1M0). Other investigations included 2D-ECHO which showed a left ventricular ejection fraction (LVEF) of 55%.

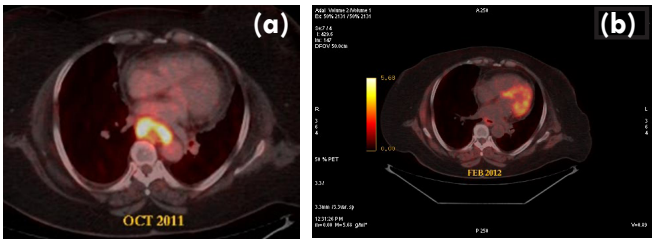

Fig.1(a): Fused axial image showing esophageal wall thickening with increased FDG uptake. (before treatment). **(b):** Fused axial image, corresponding to figure 1A showing near complete metabolic resolution, with regression in wall thickening (after treatment).

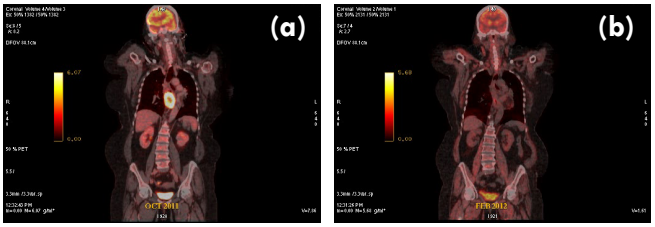

Fig.2(a): Coronal fused image showing esophageal lesion with increased FDG uptake (before treatment). **(b):** Coronal fused image, corresponding to figure 2A showing near complete metabolic resolution with regression in wall thickening (after treatment).

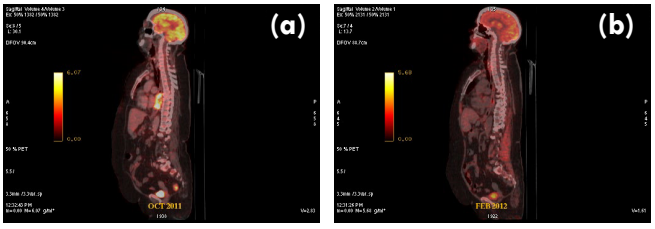

Fig.3(a): Sagittal fused image showing esophageal lesion with increased FDG uptake (before treatment). **(b):** Sagittal fused image, corresponding to figure 3A showing near complete metabolic resolution with regression in wall thickening (after treatment).

In view of the patient's general condition (i.e. age and obesity) and the advanced nature of the disease a non-surgical intervention was decided in this patient, which included concurrent chemoradiation along with nimotuzumab 200 mg. The chemotherapy was with cisplatin in the dose of 35 mg/m^2 weekly for a period of seven cycles and radiotherapy was with a total radiation dose of 59.5 Gy. Chemoradiation has known toxicities and in an attempt to reduce this, cisplatin alone was used with radiotherapy and nimotuzumab.

The patient responded favourably, which was evident on a repeat, post-treatment whole body PET-CT scan. The images showed mild focal increased FDG uptake along the distal esophageal lumen at the level of D8 vertebra and small lymph nodes with no abnormal FDG uptake in pre-vascular space along the arch of aorta, pre-cranial and left hilar regions (see figure 1B, 2B and 3B below depict the same). Patient tolerated the therapy well without any significant adverse effects.

Discussion

As mentioned earlier there is no single modality therapy which has proved to be effective in the treatment of esophageal cancer. This led to the development of definitive chemoradiotherapy paradigms. Several agents including 5-fluorouracil (5-FU), cisplatin, and mitomycin C (MMC) have shown to be beneficial in this regard. Nonetheless, despite bringing dramatic improvement in survival, chemotherapy is associated with significant toxicity. This gives scope to explore better treatment options like incorporating targeted biologic agents which have tumor specific activity and decreased systemic toxicity. There are multiple tumor biomarkers which can act as targets. Amongst them, most frequently, EGFR is overexpressed in about 92% of esophageal cancer [4]. There are many studies which have shown the effectiveness of anti-EGFR therapy in various epidermal cancers. Cetuximab (chimeric) and panitumumab (murine) have been commonly used. However, serious adverse events have been reported with these monoclonal antibodies due to their antigenicity [2].

Nimotuzumab (h-R3) is a newer, humanized monoclonal antibody, which has a replaced murine complementary determining regions (CDR) and human origin antibody backbone. In the preclinical study, h-R3 showed significant anti-tumor, pro-apoptosis and anti-angiogenesis activities [5]. It is well tolerated and has shown proven efficacy in the treatment of advanced squamous cell carcinomas of the head and neck and high grade glioma. The adverse reaction profile is also encouraging with absence of severe side-effects in comparison to other approved anti-EGFR antibodies. Nimotuzumab has been previously used with chemotherapy in various settings with good response to the combination. A pilot study conducted by Yan Ling *et al.* in China with a sample size of 19 patients with advanced esophageal cancer found better response rate (42.1%) and Disease Control Rate (68.4%) with nimotuzumab [6]. Another study by Zhang *et al.* compared nimotuzumab plus paclitaxel and cisplatin as first-line treatment for esophageal squamous cell cancer in 55 patients. There was a favourable response similar to the previous study with partial response (PR) in 14 (63.6%), stable disease (SD) in 7 (31.8%) and DCR of 95.4% [7].

Nimotuzumab has also been tried in combination with radiotherapy alone in a few settings. A study by Wang *et al.* in 42 patients with esophageal cancer used nimotuzumab in the dose of 200 mg with RT (50-70 GY). The response rates were as follows: CR- 9.5%, PR- 50%, SD- 4.8% and DCR- 64.3%. A median survival time (MST) of 14 months was noted with a one year survival benefit of 54.8% and nimotuzumab was well tolerated with no serious adverse events [8]. Analysing the role of nimotuzumab in these settings, a hypothesis was formulated to look for the

beneficial effects of nimotuzumab in combination with chemoradiotherapy. Cisplatin is a potent cytotoxin and radio sensitizer, when combined with radiotherapy; the differential DNA damage of the combined modalities overwhelms DNA repair mechanisms for synergistic cytotoxicity, even in radio resistant hypoxic cells [3]. Nimotuzumab has shown to improve the effectiveness in combination with these treatment modalities. However, there is very little data to support the same. One such study by Ramos-Suzarte M *et al*. in 63 patients with non-resectable esophageal carcinoma, Nimotuzumab 200 mg was used for 6 weeks with cisplatin (75 mg/m^2), 5-FU (750 mg/m^2) and RT - 45 GY. An ORR of 47.8% as compared to 15.4% in the control group (*P*-value=0.014) was noted. The DCR was 60.9% (*P*-value=0.017). Nimotuzumab was well tolerated with no serious adverse events [4].

Similarly in our study, the patient responded well to the combination by showing a near absence of tumor lesion, which was evident on a repeat, post treatment whole body PET-CT Scan. The images (figure 1B, 2B and 3 B) showed mild focal increased FDG uptake along the distal esophageal lumen at the level of D8 vertebra and small lymph nodes with no abnormal FDG uptake.

Conclusion

Our case study is one such example which depicts a positive role of nimotuzumab in treatment of esophageal squamous cell carcinoma. However, more studies on the use of this molecule in a similar setting on a larger population of patients will play a crucial role in evolving the treatment paradigm for advanced esophageal squamous cell carcinoma.

References

1. WHO GLOBOCAN 2012, Estimated cancer incidence, mortality and Prevalance worldwide in 2012. Available at: http://globocan.iarc.fr/factsheets/cancers/oesophagus.asp. Accessed on 10 March 2015.
2. DeVita VT Jr, Lawrence TS, Rosenberg SA. Cancer: Principles & Practice of Oncology. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
3. Neuner G, Patel A, Suntharalingam M, Chemoradiotherapy for Esophageal Cancer. Gastrointest Cancer Res. 2009;3(2):57-65.
4. Ramos-Suzarte M, Lorenzo-Luaces P, Lazo NG, Perez ML, Soriano JL, Gonzalez CE, *et al*. Treatment of malignant, non-resectable, epithelial origin esophageal tumors with the humanized anti-epidermal growth factor antibody nimotuzumab combined with radiation therapy and chemotherapy. Cancer Biol Ther. 2012;13(8):600-605.
5. Rodríguez MO, Rivero TC, del Castillo BR, Muchuli CR, Bilbao MA, Vinageras EN, *et al*. Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck. Cancer Biol Ther. 2010;9(5):343-349.
6. Ling Y, Chen J, Tao M, Chu X, Zhang X. A pilot study of Nimotuzumab combined with cisplatin and 5-FU in patients with advanced esophageal squamous cell carcinoma. J Thorac Dis. 2011;4:58-62.
7. Zhang X, Lu M, Wang X, Li J, Li Y, Li J, *et al*. Nimotuzumab plus paclitaxel and cisplatin as first-line treatment for esophageal squamous cell cancer: A single center prospective clinical trial. J Clin Oncol. 31, 2013 (suppl; abstr 4097).
8. Liang J, E M, Wu G, Zhao L, Li X, Xiu X, *et al*. Nimotuzumab combined with radiotherapy in esophageal cancer: Preliminary study of a phase II clinical trial. Onco Targets Ther. 2013;6:1589-1596.