Excellent Response with Chemoradiotherapy Followed by Short Course Adjuvant Nivolumab (Nivolunix ®) in a Patient with Locally Advanced Cancer of Esophagus

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Abstract

Primary esophageal and esophagogastric junction tumors are a common group of tumors in Africa with a high incidence in Kenya. Chemotherapy and radiotherapy are the main therapy options for advanced inoperable tumors. However, immune checkpoint inhibitor therapy is gaining prominence in this group of tumors. Tumors with high PD-1/PD-L1 expression, high microsatellite instability, and negative Herceptin status are the most beneficiaries of ICI therapy. Several studies outlined the first-line as well as second-line use of ICI therapy in this group of tumors. We are presenting a case of a locally advanced inoperable tumor, successfully treated with combined modality therapy including concurrent chemo radiotherapy followed by short-course adjuvant immunotherapy in a lower esophageal, esophagogastric junction tumor. The patient remained in complete response for two years since completion of therapy and is on close follow-up.

Keywords: Esophagogastric tumour • Nivolumab • Concurrent chemoradiotherapy • Immune checkpoint inhibitor therapy

Introduction

Esophageal Cancer (EC) remains a major concern regarding morbidity and mortality. It ranks as the sixth most common cause of cancer-related mortality and the seventh most common cancer globally [1]. Kenya has one of the highest incidences of EC not only in Africa but also across the globe [2]. With an incidence of 17.6 per 100,000, it is the fourth leading cause of cancer-related deaths after breast, cervical, and prostate [2,3]. Squamous Cell Carcinoma (SCC) accounts for the majority of esophageal cancers roughly 80% while Adenocarcinoma accounts for about 20%, however, adenocarcinomas are becoming more common especially in Western countries [4]. In Kenya, SCC still forms the majority accounting for 90%. Alcohol consumption, dietary change/food preparation, very hot foods/drinks, and genetic factors are major risk factors for EC in Kenya [2]. The majority of patients with esophageal cancer are diagnosed late. Most of them undergo palliative treatment, with a survival rate of around 5% [5]. Immunotherapy is becoming a game changer in the treatment of various cancers and Immune Check Point Inhibitors (ICI) are now approved for the treatment of esophageal cancer as per The National Comprehensive Cancer Network (NCCN) [6]. We report a case of locally advanced cancer of the esophagus. The patient achieved a complete response with adjuvant Nivolumab post Concurrent Chemo-radiotherapy (CCRT).

Case Presentation

A 69-year-old man, presented with progressive dysphagia for 7 months. He underwent standard laboratory investigations including an OGD that found a large fungating circumferential centrally ulcerated tumor at 25 cm-30 cm, causing partial occlusion. Histology was well-differentiated Squamous Cell Carcinoma (SCC). Computed tomography of the chest demonstrated an irregular left-sided esophageal thickening spanning T9-T11,5 cm long mass that has direct continuity with a large (42 mm) nodal mass which was adherent to the aorta, multiple mediastinal and subphrenic nodes with a 2.7 cm subcarinal node adherent to the main bronchus. No distant metastasis was visualized. PET CT showed a 6 cm metabolically active mid-to lower esophageal mass with wall thickening between T7-T10, metabolically active left retro clavicular, para-esophageal, mediastinal, and gastro-hepatic adenopathy (Figure 1A-1C). Based on the workup, the patient was diagnosed to have a locally advanced tumor of the mid to lower esophagus and the esophagogastric junction of TNM stage cT4N3M0 (Stage IVA- AJCC 8th Edition). Further studies confirmed high PDL1, HER2 negative, MSI unstable tumor. He was seen at a tertiary private hospital and was started on chemotherapy with Capecitabine-Oxaliplatin (Cape Ox) regimen. He completed 3 cycles with no subjective improvement rather he developed moderate to severe toxicity. The patient could not continue with the suggested therapy and reported to us for a second opinion. He was recommended to undergo Concurrent Chemo-radiotherapy (CCRT) with weekly Carboplatin (AUC2) and Paclitaxel (75 mg/m^2) followed by adjuvant Nivolumab. He received a total dose of 5040 cGy in 28 fractions and 5 weekly cycles of Carboplatin-Paclitaxel. IMRT technique was used for radiotherapy to the primary tumor and nodal stations. The CCRT was completed on 4th May 2021 and was well tolerated. He was then started on adjuvant Nivolumab 480 mg every 28 days, of which he completed 6 cycles, the last in December 2021. Further therapy was withheld due to logistic reasons. The patient responded extremely well and his quality of life improved significantly. Post therapy he was able to feed well and gained back his weight. PET CT done 6 months after completion of immunotherapy showed complete tumor response to the primary with a small avid subcarinal node. He was advised to take 6 months of oral capecitabine therapy which he managed to take for 3 months only since he could not tolerate it further. In January 2023 he was seen in the clinic for his regular follow-up and was clinically free of disease. PET CT requested a complete response to the primary, with only a small FDG avid celiac node that was kept under close observation (Figure 1D-1F).

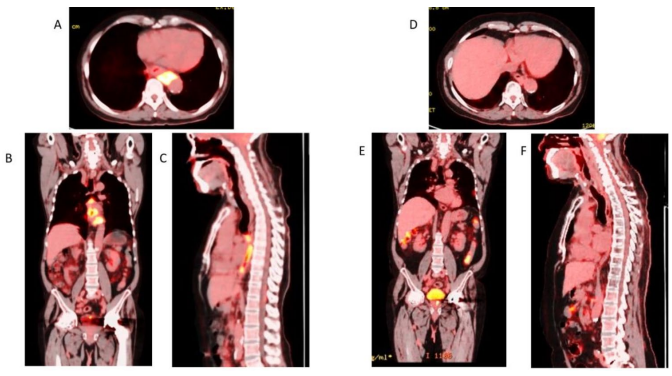

Figure 1. (Left- A-C) Pre-treatment and (D-F) Post-treatment PET CT images in axial, coronal, and sagittal planes showing complete resolution of esophageal cancer lesion.

Discussion

EC has a high mortality rate, with 90% of patients dying within five years of diagnosis. This is partly due to the fact that the disease is often diagnosed at an advanced stage when treatment options are limited [4-6]. Immunotherapy is an emerging treatment option for cancer, including locally advanced cancer of the esophagus. The main type of immunotherapy used in cancer treatment is immune checkpoint inhibitors. These drugs work by releasing the "brakes" on the immune system, allowing it to recognize and attack cancer cells more effectively [7].

Several clinical trials have evaluated the use of ICI for locally advanced EC, both alone and in combination with other treatments such as chemotherapy and radiation therapy. While results have been mixed, some studies have shown promising outcomes, particularly in patients whose tumors express high levels of certain immune biomarkers.

The Checkmate 648 study evaluated the combination of two immunotherapy drugs, Nivolumab and Ipilimumab, compared to chemotherapy in patients with previously untreated advanced or metastatic gastric cancer or Gastroesophageal Junction (GEJ) cancer. The results of the study found that the combination of nivolumab and ipilimumab improved overall survival compared to chemotherapy in patients with previously untreated advanced or metastatic gastric cancer or GEJ cancer. The median overall survival was 13.7 months for the nivolumab and ipilimumab group compared to 9.1 months for the chemotherapy group. The progression-free survival was also significantly better in the nivolumab plus chemotherapy than chemotherapy alone [8].

Based on the Attraction-3 trial, the FDA approved nivolumab in 2020 for use in patients with esophageal SCC who have previously received fluoropyrimidine-based and platinum-based chemotherapy irrespective of PD-L1 expression status [9].

Another important study, a phase 3 clinical trial (Keynote-590) evaluated the combination of Pembrolizumab and chemotherapy compared to chemotherapy alone as first-line therapy in patients with advanced or metastatic esophageal cancer. The results of the study showed that the combination of Pembrolizumab and chemotherapy significantly improved overall survival compared to chemotherapy alone. The median overall survival was 12.4 months in the Pembrolizumab and chemotherapy group compared to 9.8 months in the chemotherapy alone group. The combination therapy also showed a higher Overall Response Rate (ORR) of 45.0% compared to 29.3% in the chemotherapy-alone group. The combination therapy also demonstrated a longer Progression-Free Survival (PFS) with a median of 6.3 months compared to 5.8 months in the chemotherapy-alone group. Based on these results, the study authors concluded that the combination of Pembrolizumab and chemotherapy should be considered a new standard of care for the first-line treatment of advanced or metastatic esophageal cancer [10].

In view of the excellent results from the studies investigating the role of immunotherapy in advanced EC, it was decided to give our patient the benefit of immunotherapy with ICI Nivolumab. This led to impressive results with radiologic complete response in the primary as evidenced by the post-treatment PET-CT.

Despite the encouraging results of immunotherapy in oncology, its use is limited due to a few factors such as its prohibitively high cost, especially in low-middle-income countries. Apart from the financial toxicity of immunotherapy, immune-related adverse events are also a crucial aspect to consider when deciding on incorporating ICI in the management of EC. The symptoms of Immune-related Adverse Events (irAEs) can vary depending on the affected organ or tissue, but some common examples include rash, diarrhea, colitis, hepatitis, thyroid dysfunction, pneumonitis, and adrenal insufficiency. These side effects can range from mild to severe and can occur at any time during treatment or even after treatment has ended.

Conclusion

Immunotherapy is an emerging treatment option for cancer, including locally advanced cancer of the esophagus. Some studies have shown promising results, particularly in patients whose tumors express high levels of certain immune biomarkers. It is important to note, however, that immunotherapy is not suitable for all patients with locally advanced esophageal cancer. Treatment decisions should be made on a case-by-case basis, taking into account factors such patient's general physical condition, co-morbidities, support system, and tumor characteristics.

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