Asian Pacific Journal of Cancer Care
Vol 8 No 3 (2023), 455-458
Original Research

Combined Metronomic Chemo-Immunotherapy in Metastatic Carcinoma of Esophagus in Second Line and Beyond

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Background and Aims: Approximately 570,000 new cases are diagnosed with esophageal cancer worldwide annually and approximately 510,000 deaths from this disease per year. There are currently no effective second-line treatments for patients who progress on cisplatin and 5-fluorouracil. Esophageal squamous cell carcinomas and adenocarcinomas have proven to be inherently resistant to systemic treatments as a result of histological, molecular and etiological heterogeneity, with limited responses seen after first line therapy.
Methods: We are presenting 3 case reports of 57 year old man, 53 year old man & 47 year old woman who, presented with dysphasia for solid foods, weight loss and dyspepsia since 1 month, 3 months & 1.5 months respectively. Upper gastro oesophageal endoscopy shows ulcerated friable lesion with minimal luminal compromise with biopsy showing poorly differentiated adenocarcinoma (PDAC) and PECT-CT showed FDG avid lesions in gastroesophageal junction, gastric cardia, multiple retroperitoneal lymph nodes and bilateral liver lesions. All 3 were having stage IV disease, with PDAC, squamous cell carcinoma & PDAC respectively. We have started 1st patient on DOX regimen containing Docetaxel, Oxaliplatin and Capecitabine at an interval of 2 weeks and after 4 cycles he was having stable disease in GE junction, liver and slightly increased size of retroperitoneal lymph nodes. Second & 3rd patient was put on Pclitaxel-carboplatil protocol, after 6 cycles both were having partial response & was managed with 6 cycles CAPOX as second line che otherapy. After 5th & 6th months of second line chemotherapy both patients were having progressive disease.
Results: In view of radiological progression we started him on Injection, Nivolumab 240mg intravenously every 2 weekly along with low dose capecitabine 500mg twice a day. After 4 cycles of treatment his PET-CT showing complete metabolic response in GE junction, liver and retroperitoneal lesions. Now we are continuing Nivolumab and low dose capecitabine planned to complete for 2 years.
Conclusion: So to conclude nivolumab along with metronomic chemotherapy with low dose capecitabine was very well tolerated and exhibited antitumor activity in extensively pretreated patient with metastatic esophageal poorly differentiated adenocarcinoma. Additional studies of Nivolumab and metronomic chemotherapy and immuno-immuno combination therapy in these diseases are ongoin.

Introduction

The promise of immunotherapy in esophago-gastric cancer has been suggested for a long time due to the recognized link between infection, chronic inflammation, and malignancy. The emerging clinical trial data is somewhat confusing but it appears that anti programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) monoclonal antibodies do demonstrate some efficacy in a minority of gastroesophageal cancer patients with metastatic disease. Recent phase III data from the Keynote 059 and Attraction 2 studies demonstrate response rates of approximately 12% in a population of heavily pretreated patients and there was an overall survival benefit in the Attraction 2 trial [1,2].

Promising immunotherapy approaches, such as chimeric antigen receptor (CAR) T cell therapy and therapeutic blockade of immune checkpoints, in particular cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 pathway (PD-1/ PD-L1), have boosted the development of new therapeutic regimens for patients with metastatic esophageal cancer. Immune blockade of the PD-1/PD-L1 interaction by monoclonal antibodies can restore the antitumor activity of cytotoxic T cells. Early clinical trials using two anti-PD-1 antibodies (nivolumab and pembrolizumab), and three anti-PD-L1 antibodies (avelumab, durvalumab, and atezolizumab), have shown great promise [3].

Case Vignette

Fifty-seven-year-old man with history of diabetes, non-smoker and non-alcoholic by habits came with history of dysphagia for solid foods, weight loss and dyspepsia for 1 month. On examination there was mild pallor and moderate hepatomegaly. His routine investigations revealed hemoglobin of 10.3gm/dl, total count of 8700/ cu mm and platelet count of 292000/cu.mm. Erythrocyte sedimentation rate (ESR) was 70mm at first hour. Serology for human immunodeficiency virus, hepatitis B and C viruses were negative.

Upper gastro esophageal endoscopy shows ulcerated friable lesion at GE junction with minimal luminal compromise and biopsy was taken. His histopathology of gastro-esophageal biopsy specimen shows poorly differentiated adenocarcinoma and on Immunohistochemistry the tumor cells are diffusely positive for CK7 and show focal positivity for CEA and tumor cells are negative for P40 and P63. Computed Tomography (CT) scan of thorax and abdomen-pelvis shows heterogeneously enhancing circumferential wall thickening involving gastro-esophageal junction with few metastatic hypodense lesions showing heterogeneous enhancement in segment VII of right lobe of liver, in segment IVA and II of left lobe of liver along with peri-gastric and paraaortic lymphadenopathy. PET-CT shows FDG avid asymmetric gastric / gastroesophageal junction wall thickening up to 17mminvolving its cardia and extending up to GE junction with standard uptake value (SUV) – 10.8, multiple FDG avid lymph nodes are seen in gastro-hepatic, portocaval, peri-caval, peri-aortic and aorto-caval region and the largest measuring 22x13mm in aorto-caval region with SUV - 13.2 and multiple FDG avid heterogeneously enhancing focal lesions are seen in both lobes of liver, the largest measuring 33x31 mm in segment IV with SUV - 15.

Patient was managed with supportive care and the definitive treatment was done with DOX regimen containing Inj. Docetaxel 60mg per m2 IV on D1, Inj.

Oxaliplatin 100mgper m2 IV on D1 and Tab. Capecitabine 1000mg per m2 orally twice daily continuously with cycles repeated every 2 weekly. After 4 cycles of DOX regimen, CT scan of thorax and abdomen-pelvis shows stable disease in GE junction, liver and slightly increased size of retroperitoneal lymph nodes of around 18%. In view of radiological progression, after explaining about new treatment, we started him on Injection, Nivolumab 240mg intravenously every 2 weekly along with metronomic low dose capecitabine at 500mg twice daily regimen. After completion of 4 cycles of treatment his PET-CT showing significant interval reduction in soft tissue thickening and

FDG uptake of lesion in gastric cardia and GE junction is noted with minimal soft tissue thickening in distal esophagus with no significant metabolic activity. Near total resolution of FDG avid liver lesions and lymph nodes in gastro hepatic ligament, porto- caval, peri caval, peri aortic and aorto caval region is noted. In view of very good response to combined Nivolumab and metronomic chemotherapy, we are continuing Nivolumab 240mg and low dose capecitabine at an interval of 2 weeks and planned to complete for 2 years or till progression of the disease. Now he is on regular treatment with 2 weekly nivolumab and metronomic chemotherapy and at the time of submission of this article he was completed 11^{th} cycle of immunotherapy. Patient tolerated immunotherapy, very well without much intolerable side effects. Now he is continuing the same dose and schedule of nivolumab.

Second and third patients are, 53 year old man & 47 year old woman who, presented with dysphasia for solid foods, weight loss and dyspepsia since, 3 months & 1.5 months respectively. Upper gastro oesophageal endoscopy of both patients shows ulcerated friable lesion with minimal luminal compromise. Both patients were having stage IV disease, with squamous cell carcinoma & PDAC respectively. Second & 3rd patient was put on Pclitaxel-carboplatil protocol, after 6 cycles both were having partial response & was managed with 6 cycles CAPOX as second line chemotherapy. After 5^{th} & 6^{th} months of second line chemotherapy both patients were having progressive disease. In view of radiological progression, we started both patients on Injection, Nivolumab 240mg intravenously every 2 weekly along with low dose capecitabine 500mg twice a day. After 4 cycles of treatment both the patients PET-CT showing complete metabolic response in GE junction, liver and retroperitoneal lesions. Now we are continuing Nivolumab and low dose capecitabine planned to complete for 2 years.

Discussion

Esophageal cancer (EC) is the sixth most common cause of cancer-related death worldwide, with a 5-year survival rate of 5%–8% in patients with metastatic disease. First–line platinum-based doublet chemotherapy (CTX) provides a modest survival benefit in patients with metastatic squamous cell EC (mESCC), with a median OS of 7.6 months. Over 40% of patients with EC have PD-L1+ tumors, which are associated with worse OS outcomes. Nivolumab has received FDA approval for treatment of patients with several malignancies, including advanced lung cancer, melanoma, advanced kidney cancer, head and neck squamous cell cancer, advanced liver cancer, advanced bladder cancer, classical Hodgkin lymphoma and colorectal cancer. Nivolumab (NIVO), an anti–PD-1 mAb, demonstrated efficacy and a manageable safety profile in patients with ESCC. In the phase 2 ATTRACTION-1 trial, NIVO 3 mg/kg produced an ORR of 17% and median OS of 10.8 months in heavily pretreated patients with ESCC [4]. The programmed death-1 (PD-1) pathway is an immune checkpoint to attenuate T-cell–mediated immune responses and may be exploited by tumors to avoid immune surveillance. Immune blockade of the PD-1/PD-L1 interaction by monoclonal antibodies can restore the antitumor activity of cytotoxic T cells [5].

Results from a randomized, phase III study presented at 2017 Gastrointestinal Cancers Symposium, Investigators concluded that nivolumab was effective as the salvage treatment in pretreated patients with advanced gastric or gastro-esophageal junction cancer. It is the first randomised, phase III trial in which immunotherapy agent demonstrated improved survival in the setting in which currently there is no standard of care treatment [2].

In the international, multicenter, open-label, randomized ATTRACTION-3 trial, approximately 390 patients with esophageal cancer who were refractory to or intolerant of 1 prior combination therapy with fluoropyrimidine and platinum-based treatment received either nivolumab at 240 mg/body solution intravenously (IV) every 2 weeks or chemotherapy with docetaxel or paclitaxel until disease progression or severe adverse events (AEs). Docetaxel was administered at 75 mg/m^2 IV every 2 weeks and paclitaxel at 100 mg/m2 weekly for 6 weeks followed by a 2-week treatment holiday. Preliminary results showed that the ORR was 17.2% (95% CI, 9.9%-28.2%) as of May 17,

2015. With the 2-year update, the ORR was 17.2% and the median DOR was 11.7 months. Kaplan-Meier estimates for 1-, 1.5-, and 2-year OS rates were 45.3%, 25.0%, and 17.2%, respectively. One-, 1.5, and 2-year PFS rates were 10.3%, 8.6%, and 8.6%, respectively [6].

One clinical trial with trial no NCT03278626, A Phase I/II Open Label Multi-Center Study of Immune Checkpoint Therapy With Nivolumab for Patients With Locally Advanced Esophageal Squamous Cell Carcinoma comparing role of Nivolumab along with concurrent chemo-radiotherapy with weekly Paclitaxel 50mg per m2 and Carboplatin AUC 2 along with radiation therapy will tell us the added role of nivolumab in locally advanced ESCC.

Several trials are currently studying the use of combination immune checkpoint inhibitors. The ongoing Checkmate-649 study [7] is assessing dual immune checkpoint inhibitors nivolumab plus ipilimumab versus combination chemotherapy (XELOX or FOLFOX) versus FOLFOX plus nivolumab in the first line setting of metastatic gastric or GEJ cancers (NCT02872116). The BMS Fraction-study (Fast Real-Time Assessment of Combination Targeted Immuno-Oncology) is a basket study assessing multiple IO-IO combinations including the combination of nivolumab plus ipilimumab, nivolumab plus relatlimab (LAG-3 inhibitor) or nivolumab plus BMS-986205 (IDO inhibitor) in advanced gastric/GEJ cancer (NCT 02935634). Similarly, the Roche-Genentech Morpheus study is an open-label umbrella study evaluating multiple immunotherapy based treatment combinations in patients with locally advanced, unresectable or metastatic gastric or GEJ cancers (NCT 03281369).

In conclusion, we clearly need a much greater immunologic/molecular understanding of biological phenomena that lead to the development and progression of esophageal cancer and a comprehensive analysis of the immune microenvironment not just in the metastatic setting but at various stages throughout a cancers lifespan. If single agent chemotherapy is a better strategy than single agent PD-1 inhibitors for the majority of patients then we clearly need to look at IO-IO combination strategies or combining PD-1 inhibitors with chemotherapy. These studies are ongoing and preliminary results are promising but the science needs to guide our clinical trial designs. We conclude that Nivolumab showed promising activity with a manageable safety profile. This drug could offer a potential new treatment approach for patients with treatment-refractory advanced esophageal carcinoma.

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