Case Report

Maximizing response: a case report of salvage chemotherapy after immune checkpoint inhibition in a patient with previous chemo-refractory metastatic esophageal carcinoma

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Abstract: Esophageal carcinoma is an aggressive malignancy and outcomes remain poor. Immune checkpoint inhibitors are a standard-of-care in the third-line and beyond settings, although benefit is modest. Herein, we report the case of a patient who achieved a partial response to salvage chemotherapy following treatment with an immune checkpoint inhibitor despite having chemo-refractory disease. A 41-year-old male, with a history of Crohn's disease, was diagnosed with Her2-positive metastatic esophageal adenocarcinoma to lungs and lymph nodes. The patient received multiple lines of systemic therapy including: first-line modified DCF (docetaxel/cisplatin/5-fluorouracil) with trastuzumab, second-line trastuzumab/afatinib on a clinical study, third-line carboplatin/irinotecan/ramucirumab and fourth-line treatment with a Her2 antibody-drug conjugate, DS-8201A, on a phase I study. While the patient was not a candidate for clinical trials evaluating immune checkpoint inhibitors due to his history of Crohn's disease, the latter was well controlled. Thus, the patient commenced pembrolizumab as fifth-line of treatment 2 years since diagnosis. After 3 cycles of therapy, the patient developed grade 3 immune-related colitis and treatment was discontinued. The patient maintained a good performance status and commenced a sixth-line of carboplatin/irinotecan/ramucirumab. Subsequent imaging demonstrated a partial response which was maintained over a 6-month period. This case demonstrates a response to previously administered chemotherapy following immune checkpoint inhibitor therapy, despite prior progression on this chemotherapy regimen. To our knowledge, this has not been previously reported in esophagogastric carcinoma (EGC). Post-immune checkpoint inhibitor chemotherapy may be a feasible treatment strategy. Research is needed to evaluate the role of post-immune checkpoint inhibitor chemotherapy in patients with metastatic EGC.

Keywords: Esophagogastric carcinoma (EGC); metastatic; Her2; trastuzumab; checkpoint inhibitor; PD-L1; pembrolizumab; Crohn's disease; adalimumab

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Introduction

Esophageal carcinoma is an aggressive malignancy with approximately 50% of patients having metastatic disease at diagnosis (1). Doublet chemotherapy with fluoropyrimidine/platinum remains the standard first-line treatment for metastatic esophageal cancer, with the addition of trastuzumab for Her2-positive tumors (1,2). Ramucirumab, an anti-vascular endothelial growth factor receptor-2 antibody, is active as monotherapy and combined with paclitaxel chemotherapy in the second-line setting.

Immune checkpoint inhibitors (ICIs) have recently been incorporated into the treatment paradigm (3,4), although benefit is modest in unselected patients. Currently, there are no data to suggest any benefit for recycling prior chemotherapy after ICIs exposure in esophagogastric carcinoma. Herein, we report the case of a patient who achieved a partial response to a salvage chemotherapy regimen following treatment with an ICI, in the context of inactive inflammatory bowel disease, despite having previous chemo-refractory disease.

Case presentation

We report the case of a 41-year-old gentleman who presented in March 2015 with a 3-week history of progressive dysphagia and 4 kilograms weight loss. His past medical history was notable for Crohn's disease, which was diagnosed two and a half years prior and had been managed with adalimumab, an anti-tumor necrosis factor-α antibody. A colonoscopy 6 months prior to his diagnosis was unremarkable and the patient was asymptomatic at the time of his cancer diagnosis; adalimumab was therefore discontinued at this time. His ECOG performance status was 1 on initial presentation. A computed tomography (CT) scan demonstrated irregular soft tissue thickening in the proximal esophagus, with surrounding tissue induration, inseparable from the trachea anteriorly and upper thoracic vertebrae posteriorly. There were numerous bilateral lung nodules consistent with metastases and bilateral supraclavicular adenopathy.

An esophagogastroduodenoscopy (EGD) revealed a tumor in the mid esophagus and biopsy confirmed moderately differentiated adenocarcinoma. Immunohistochemistry (IHC) for Her2 was 2+ (equivocal) but reflexive fluorescence in situ hybridization (FISH) testing revealed a Her2/CEP17 ratio of 4.0, consistent with Her2 positive disease (5). DNA mismatch repair (MMR) proteins tested by IHC were retained (MMR intact) (6). Next generation sequencing with the MSK-IMPACT platform was performed and revealed a *TP53* mutation (7). A total of seven mutations were detected (*NF1* X771_splice, *RB1*, *TP53*, *NF1* D1059N, *PGR*, *HNF1A*, *DOT1L*) plus an *ERBB2* amplification.

The patient received first-line modified DCF (docetaxel/cisplatin/5-fluorouracil) and trastuzumab. After 9 months of disease control, repeat CT imaging in January 2016 demonstrated an increase in the size and number of lung lesions. Following a lung biopsy which confirmed persistent Her2 positivity, the patient enrolled in a single-arm phase II study evaluating the combination of trastuzumab and afatinib (NCT01522768), an irreversible inhibitor of the ErbB family (8). Repeat MSK-IMPACT testing was performed on lung biopsy tissue and revealed a *PIK3CA* mutation. There were twelve mutations (*PIK3CA*, *IL7R*, *MITF*, *BRD4* Q515H, *BRD4* Q517L in addition to those listed above) detected in total.

CT imaging in April 2016 demonstrated progression of disease on study. The patient was deemed not a candidate for a clinical trial (e.g., the KEYNOTE-059 study) (3) evaluating ICIs given his history of Crohn's disease. He then received third-line chemotherapy with carboplatin/irinotecan/ramucirumab. The patient achieved a partial response to this treatment regimen, with resolution of the right pleural effusion and decrease in thoracic adenopathy and bilateral pulmonary metastases. After 1 year of disease control, his CT imaging in April 2017 demonstrated further disease progression, with enlargement of pulmonary and mediastinal nodal metastases. He subsequently enrolled on a phase I study evaluating a Her2 antibody-drug conjugate, DS-8201A (9). Interval imaging on study demonstrated evidence of progression with an increase in thoracic and mediastinal adenopathy.

The patient then started a fifth-line treatment with pembrolizumab as part of a compassionate access program. His PD-L1 status was not determined. His Crohn's disease was well-controlled, without symptoms or requirement for any medications in the entire time he had received cytotoxic chemotherapy. After 3 cycles of treatment with pembrolizumab, he developed grade 2 diarrhea (5–6 bowel motions per day) associated with one episode of blood mixed with stool. A trial of budesonide was recommended by our gastroenterology colleagues. His symptoms however progressed to grade 3 colitis and he was hospitalized. A colonic biopsy demonstrated active enteritis with features suggesting immune-mediated injury. The patient was commenced on intravenous methylprednisone 2 mg/kg with excellent symptomatic relief. After 48 hours the patient was transitioned to oral prednisone 200 mg daily in divided doses. Prednisone was slowly tapered over a 6-week period. Due to recurrent symptoms prednisone 20 mg was recommenced along with adalimumab 40 mg every 2 weeks and with resolution of symptoms prednisone was successfully tapered. A follow-up CT in August 2017 showed further progression of his lung metastases and thoracic nodes.

Despite the progression of disease, the patient continued to have a good performance status, with minimal cancer-related symptoms. Having experienced relatively slow progression on carboplatin/irinotecan/ramucirumab previously, it was recommended that he recommence this treatment regimen as sixth-line therapy. Interval CT imaging after 2.5 months of treatment in November 2017 demonstrated a partial response to treatment, with a decrease in size of his metastatic lesions. Mediastinal nodes decreased from 3.2 cm × 2.9 cm to 2 cm × 1.8 cm and from 2.9 cm × 2.2 cm to 2 cm × 1.8 cm. A right pulmonary lesion decreased from 4.3 cm × 3.9 cm to 3.3 cm × 3.2 cm. The patient's disease remained stable for 6 months after starting sixth-line chemotherapy. However, he subsequently developed progressive pulmonary disease and died 8 months after commencing salvage chemotherapy. This case demonstrates a remarkable response to a salvage chemotherapy regimen following treatment with an ICI, despite the patient having previously progressed on this chemotherapy.

Discussion

Esophageal cancer is a highly lethal malignancy. Approximately 50% of patients present with overt metastatic disease for which chemotherapy remains the core treatment, aiming to palliate symptoms and prolong survival (1). While treatments have modestly improved over the past decade, outcomes remain poor in this aggressive disease.

The standard doublet regimen in the first-line setting for metastatic disease is a fluoropyrimidine/platinum doublet (1). The only validated 3-drug regimen is DCF (docetaxel, cisplatin and 5-fluorouracil), based on the V325 study which demonstrated modest improvement in outcomes with the addition of docetaxel to the standard doublet (10). While DCF resulted in longer preservation of patients' quality-of-life and performance status compared to cisplatin/5-fluoruracil, it was also associated with significant toxicity. A subsequent randomized phase II study of the parent regimen (used in the V325 study) versus a modified DCF regimen showed modified DCF to be significantly better tolerated and outcomes were at a minimum non-inferior (7). In Her2 amplified disease, the incorporation of trastuzumab with first-line therapy significantly improves response rates and survival, as demonstrated in the pivotal phase III TOGA trial (2). Given our patient's young age and excellent performance status, modified DCF together with trastuzumab was the recommended first-line therapy. Data to support the tolerability of this combination was suggested by an ongoing clinical study (11).

To date, no Her2-directed therapies have demonstrated efficacy in the second-line setting (12,13). Interestingly, loss of Her2 expression may occur in patients with Her2-positive esophagogastric carcinoma (14). Of 84 Her2-positive patients treated with first-line chemotherapy plus trastuzumab, 23 (27%) had post-trastuzumab biopsies. Of these, 8 (35%) were no longer Her2 positive. This may represent a possible mechanism of acquired resistance. Our patient underwent a post-trastuzumab biopsy and remained Her2 positive, thereby meeting eligibility for enrollment on trials evaluating for additional Her2 directed therapies.

While no studies to date have shown a benefit for doublet chemotherapy beyond the first-line setting, it is an option in patients who maintain a good performance status. The patient whose medical case is discussed herein received carboplatin in addition to irinotecan/ramucirumab in the third-line setting. Based on preclinical studies indicating potential synergy between irinotecan and cisplatin, phase II trials evaluated this combination in untreated metastatic esophagogastric carcinoma and reported response rates exceeding 50% (15,16). Two phase III studies have demonstrated a benefit for ramucirumab in the second-line setting. The REGARD study showed a survival benefit for ramucirumab *vs.* placebo in patients with prior progression on first-line fluoropyrimidine and/or platinum-based chemotherapy (17). Subsequently, the RAINBOW study evaluated second-line paclitaxel with or without ramucirumab (18). Response rates (28% *vs.* 16%, P=0.0001), progression-free survival (PFS) (4.4 *vs.* 2.9 months, P<0.0001) and overall survival (OS) (9.6 *vs.* 7.4 months, P=0.0169) were superior for the ramucirumab/paclitaxel arm. The activity and tolerability of this regimen has established it as the standard-of-care in the second-line setting. Because a taxane was administered in the first-line setting, irinotecan was given in combination with ramucirumab. There is no evidence to suggest that anti-angiogenic therapy is chemotherapy-specific and we believe it is a reasonable extrapolation to combine ramucirumab with other chemotherapy backbones. The phase III RAISE study provides evidence that ramucirumab is active when combined with irinotecan-based therapy. This study showed benefit for FOLFIRI/ramucirumab *vs.* FOLFIRI (biweekly

bolus and infusional 5-FU/leucovorin/irinotecan) alone in the second-line treatment of advanced colorectal cancer (19).

There has been strong interest in the evaluation of ICIs in esophagogastric carcinoma, specifically anti-programmed death-1 (PD-1) and anti-programmed death-ligand-1 (PD-L1) antibodies. Pembrolizumab is now approved in the United States for the treatment of patients with chemo-refractory gastric or gastroesophageal adenocarcinoma whose tumors express PD-L1 (3). Nivolumab showed a similar magnitude of benefit in Asian patients in the phase III ATTRACTION-2 study (4) and has been approved in Japan, regardless of PD-L1 status, as this was not found to be predictive of survival in this study.

Patients with pre-existing autoimmune conditions have been generally excluded from clinical trials evaluating ICIs, due to the potential of exacerbating underlying autoimmune disorders and the risk of compromising the therapeutic efficacy of ICIs when using immunosuppressive agents. A retrospective series of 119 patients with metastatic melanoma evaluated anti-PD-1 therapy in patients who had preexisting autoimmune disease or major toxicity with prior ipilimumab. This study suggested that patients obtained benefit from treatment at a similar rate to those without a history of autoimmune disease (20). Furthermore, while 38% of patients experienced a flare of their autoimmune disease and required immunosuppression, all six patients with gastrointestinal autoimmune diseases did not have a flare. Patients with active autoimmune-related symptoms experienced flares more frequently compared to those with clinically inactive disease. Two patients (4%) discontinued treatment due to a flare. This data suggests that anti-PD-1 therapy may be safely administered and may still achieve clinical benefit in patients with preexisting autoimmune disease. Unfortunately, in the case discussed herein, the patient experienced grade 3 colitis, requiring steroids and permanent discontinuation of pembrolizumab.

To the best of our knowledge, this case describes the first response to chemotherapy following progression on an ICI in esophagogastric carcinoma. Several recent retrospective studies in non-small cell lung carcinoma (NSCLC) have demonstrated higher than expected objective responses to chemotherapy after administration of ICIs (21-23). One study evaluated 73 patients treated with chemotherapy after PD-1/PD-L1 inhibitors, with ten patients receiving ICIs in the first-line setting (23). Fifty-three percent had an objective response to salvage chemotherapy following ICIs *vs*. a 34.9% objective response to the last chemotherapy regimen administered prior to ICIs (P=0.03). The median OS from the start of salvage chemotherapy was 8.1 months. Despite the significant difference in objective response rate, PFS was similar between groups. The authors stipulated that this might be explained by a potential lack of continuity of the immunomodulatory effects of chemotherapy. Overall, this data may support a synergistic interaction between ICIs and chemotherapy. Chemotherapy has been demonstrated to induce release of tumor antigens and emission of danger-associated molecular patterns in the tumor microenvironment during cell death (24). It can also enhance antigen presentation, upregulate expression of costimulatory molecules and down-regulate inhibitory molecules such as PD-L1 (25).

There is also a suggestion that treatment with an ICI followed by chemotherapy is a more appropriate sequence rather than chemotherapy followed by immunotherapy. The KEYNOTE-024 study evaluated pembrolizumab or pemetrexed/carboplatin in the first-line setting in patients with NSCLC and a tumor proportion score (TPS) ≥50% and allowed cross-over upon disease progression (26). A comparison of the combined PFS for first- and second-line therapy (PFS2) between the two arms has been reported (27). Sixty percent (n=91) received anti-PD-1 therapy following first-line chemotherapy while 31% (n=48) received chemotherapy following first-line pembrolizumab. PFS2 was significantly longer in patients who received first-line pembrolizumab followed by second-line chemotherapy *vs*. that of patients who received first-line chemotherapy followed by second-line pembrolizumab (18.3 *vs*. 8.4 months, P<0.01).

There is clearly a subset of patients with Her2-positive esophagogastric carcinoma who derive significant benefit from palliative systemic therapies including single agent trastuzumab, multiple chemotherapies and through clinical studies. It has been suggested that patients with *ERBB2*-amplified, RAS/PI3K wild-type tumors derive most benefit from trastuzumab-based therapy (28). As our understanding of biomarkers of response and resistance to Her2 therapy in esophagogastric carcinoma evolves, our ability to identify this subset of patients may improve.

In conclusion, this case reports the unusual occurrence of a partial response to previously administered chemotherapy following ICI therapy, despite prior progression on this chemotherapy regimen. To our knowledge, this has not been previously reported in esophagogastric carcinoma. Emerging data suggests that post-ICI chemotherapy may be a viable therapeutic strategy, due to the potential synergy from changes in the tumor microenvironment when using both

cytotoxic and immune-based agents. Therefore, a subgroup of patients may benefit from chemotherapy after receiving an ICI, even if they previously had chemo-refractory disease. Further research is needed to enhance our understanding of the underlying mechanisms for this phenomenon, as highlighted by our case, and to prospectively evaluate the utility of post- ICIs chemotherapy in patients with metastatic esophagogastric carcinoma.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Disclaimer: The case presented herein is hypothetical, based on real-world experience.

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