Editorial

# Advanced esophagogastric cancers: the making or breaking of a backbone

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Esophageal cancer is the sixth leading causes of cancer mortality worldwide (1). In North America, adenocarcinoma has become the most common histology whereas squamous remains the most common histology worldwide. While the risk factors, tumor location, biology and prognosis of these two histologies differ, the treatment of these two types in the metastatic setting is the same. Unfortunately, most patients with either histology present with advanced disease at the time of diagnosis. Consensus is lacking as to the optimal first line chemotherapy regimen in the advanced or metastatic setting. Much of the data guiding the treatment of advanced esophageal cancer are extrapolated from trials in advanced gastric cancer and trials combining esophageal and gastric cancers. The National Comprehensive Cancer Network (NCCN) guidelines give a category 1 recommendation for doublet therapy combining fluorouracil or capecitabine and cisplatin for first line treatment for advanced esophageal and gastroesophageal junction (GEJ) carcinomas (2). However, several other chemotherapy combinations are also considered acceptable and are well tolerated.

Enzinger and colleagues presented the results of the CALGB 80403 trial which was a phase II, randomized, three arm study designed to identify an optimal chemotherapy backbone for future clinical trials in esophageal and GEJ carcinomas (3). This trial, which was endorsed by the National Cancer Institute (NCI) in 2005, randomized patients to epirubicin, cisplatin, and continuous-infusion fluorouracil (ECF), irinotecan plus cisplatin (IC), or oxaliplatin, leucovorin, and bolus and infusional fluorouracil (FOLFOX). The epidermal growth factor (EGFR) inhibitor cetuximab was added to all three treatment arms in weekly doses. The primary endpoint was response rate. The secondary endpoints included overall survival, progression free survival, and toxicity. A total of 245 patients were randomized between September 2006 and May 2009, of which 91% had adenocarcinomas. In this North American trial, the vast majority of patients were of white race (96%) with Asians comprising <1% of the total study population. Esophageal and GEJ carcinomas were fairly evenly represented. The overall response rate among patients with adenocarcinomas was 60.9% for ECF plus cetuximab, 45% for IC plus cetuximab, and 54.3% for FOLFOX plus cetuximab. Median overall survival for patients with adenocarcinomas was 11.6 months for ECF plus cetuximab, 8.6 months for IC plus cetuximab, and 11.8 months for FOLFOX plus cetuximab. Given the small numbers of squamous cell carcinomas enrolled, only 23 of the anticipated 64 patients, an exploratory analysis for response and survival was performed for this population. The response rate to IC plus cetuximab in the squamous group was much lower (12.5%) than that of ECF plus cetuximab (67%) and FOLFOX plus cetuximab (60%).

Given that one of the most important goals of treatment for this incurable population is palliation of symptoms, treatment related toxicity is of utmost importance. The overall rates of grade 3–5 hematologic toxicity were similar between the three treatment arms. However, the rates of grade 3–5 gastrointestinal (GI) and metabolic toxicity were highest in the IC plus cetuximab arm. Patients receiving

FOLFOX plus cetuximab required fewer treatment modifications compared to the other two treatment arms. Also, patients receiving FOLFOX plus cetuximab had the lowest rate of treatment discontinuation due to an adverse event and the lowest rate of treatment related mortality. Patients went on to receive second line chemotherapy at similar rates across all three treatment arms. Based on these results, the authors concluded that FOLFOX was the chemotherapy backbone with the most favorable balance of efficacy and toxicity. They also asserted that the response rate of the FOLFOX and ECF treatment arms outperformed the historic response rate for the combination cisplatin plus fluoropyrimidine, adding further support to the use of FOLFOX as a standard first line regimen.

So, did the study meet its primary goal of determining an effective chemotherapy backbone for testing in future studies? Was FOLFOX compared to the best chemotherapy regimens available? Finally, have we advanced the science and care of esophageal cancer?

The CALGB 80403 trial provides additional strong evidence for the use of FOLFOX as a first line chemotherapy regimen in advanced esophageal and GEJ carcinomas. This adds to the findings of prior studies examining FOLFOX in the setting of advanced esophageal and gastric cancers (4-8). FOLFOX is a familiar and well-tolerated backbone for evaluating targeted therapies in advanced colorectal cancer. However, unlike colorectal cancer, esophagogastric cancers are comprised of two dominant histologies. A key limitation to the global generalization of this esophageal and GEJ study is that only 9% of the patients randomized in this trial had squamous cell histology. Given the limited numbers, it is unclear how efficacious FOLFOX truly is in squamous cell histology and whether it is the optimal chemotherapy backbone for that subgroup of esophageal cancers. Several studies have already successfully utilized FOLFOX as a chemotherapy backbone for evaluating targeted therapies in adenocarcinomas. The authors of CALGB 80403 were able to take the FOLFOX data and subsequently used the regimen in a multicenter randomized phase II study in patients with metastatic esophagogastric adenocarcinoma combined with ziv-aflibercept *vs.* placebo (9). Unfortunately, the addition of ziv-aflibercept did not improve the study's primary endpoint of 6-month PFS or 1 year overall survival beyond that of FOLFOX itself. Similarly, other early phase studies have safely combined FOLFOX with biologic agents including the mTOR inhibitor everolimus (10), the c-Met inhibitor tivantinib (11), and the EGFR inhibitor erlotinib (12). These trials support the authors' assertion that FOLFOX is a suitable chemotherapy backbone for future trials.

Was the best chemotherapy regimen used in order to compare the efficacy of FOLFOX? A potential criticism of this trial is the selection of the three particular chemotherapy regimens that were used. The choice of ECF in this trial could be questioned in light of the results of the REAL2 study which showed that epirubicin, oxaliplatin, and capecitabine (EOX) had a superior overall survival of 11.2 months compared to 9.9 months with ECF (13). The REAL2 study did show a lower rate of grade 3 and 4 toxicity with oxaliplatin compared to cisplatin. The current CALGB trial confirms aspects of the REAL2 trial by showing that the regimen containing oxaliplatin had similar efficacy and favorable toxicity compared to regimens containing cisplatin. However, it remains unknown how FOLFOX would compare to EOF or EOX directly.

Similarly, one could question the use of ECF as one of the three chemotherapy backbones rather than using cisplatin and fluorouracil alone, as recommended in the NCCN guidelines (2). Epirubicin gained wider use in the treatment of gastroesophageal cancers based on the work of Cunningham and colleagues reported in 2006 (14). They demonstrated that perioperative ECF was superior to surgery alone. However, the incremental benefit of adding epirubicin to other chemotherapy regimens has not been firmly established. In a correspondence to the editor, Elimova and colleagues outlined a rationale against the use of epirubicin in the treatment of esophagogastric cancers based on the lack of incremental benefit over similar chemotherapy regimens without epirubicin in the localized disease setting (15). The current study supports that argument against the use of triplet chemotherapy containing epirubicin in advanced esophagogastric cancers, but could have made an even stronger assessment of the role of epirubicin by comparing EOF (or EOX) to FOLFOX. Alternatively, removing epirubicin from the CALGB 80403 trial would have permitted a direct comparison of cisplatin plus fluorouracil to oxaliplatin plus fluorouracil. This change is unlikely to have significantly changed the conclusion of the study in favor of FOLFOX since the REAL2 trial already demonstrated the favorable toxicity profile of oxaliplatin compared to cisplatin (13). Similarly, Al-Batran and colleagues demonstrated the favorable toxicity profile for fluorouracil plus oxaliplatin compared to fluorouracil plus cisplatin in metastatic gastric cancer with similar or even favorable efficacy (5). Also, it remains to be seen whether fluorouracil, leucovorin, and irinotecan (FOLFIRI) is a suitable alternative to FOLFOX in the first

 

line setting. CALGB 80403 demonstrated inferiority of the IC chemotherapy arm in terms of efficacy and toxicity. However, the FOLFIRI regimen may yield better results. Guimbaud and colleagues demonstrated that FOLFIRI had superior efficacy and more favorable tolerability when compared to ECX for first line treatment of advanced gastric and GEJ carcinomas (16). Therefore, CALGB 80403 supports the use of FOLFOX as the preferred first line treatment in advanced esophagogastric cancers, but leaves room for further consideration of other options such as cisplatin plus fluorouracil or FOLFIRI.

In the 12 years since this study was endorsed by the NCI, have we advanced the science and care of esophageal cancer? And if so, how does CALGB 80403 fit into the current landscape? We applaud the approval of ramucirumab and trastuzumab for adenocarcinomas. However, the number of patients who benefit from these therapies pales in comparison to those for whom their use is not indicated. Ramucirumab, a recombinant monoclonal immunoglobulin G (IgG) antibody that binds to vascular endothelial growth factor (VEGF) receptor 2, showed improved survival in the second-line setting as both a single agent (17) and in combination with paclitaxel (18). FOLFOX plus ramucirumab, however, did not improve PFS in a randomized phase II study (19). Trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), utilized a non-FOLFOX backbone. The ToGA trial showed superior overall survival for first line use of trastuzumab in combination with chemotherapy compared to chemotherapy alone for advanced gastric and GEJ tumors with HER2 overexpression (20). The majority of the patients in that trial received capecitabine and cisplatin. Little is known about whether using FOLFOX as the chemotherapy backbone would have any impact on the efficacy or tolerability. The interaction between HER2 expression and treatment response was not assessed in CALBG 80403.

The last 12 years have also seen disappointments with the use of other targeted agents. Cetuximab, an anti-EGFR monoclonal antibody used in all three treatment arms in CALBG 80403, demonstrated a lack of efficacy when combined with chemotherapy in two phase 3 studies, REAL3 and EXPAND (21,22). Disappointing outcomes also occurred when Bevacizumab, a VEGF inhibitor, did not improve survival when combined with capecitabine and cisplatin (23,24). Phase III data are lacking as to whether bevacizumab combined with a FOLFOX backbone would provide more promising results.

FOLFOX remains a reliable chemotherapy option for treatment of metastatic esophageal and GEJ cancer. Is it the only backbone that should be studied going forward? Probably not given there are other effective chemotherapy options available such as the oral agent S-1, available in Asia, and given the limited data on its efficacy in squamous cell carcinomas. As we strive to move beyond the limited successes of biologic agents in esophagogastric cancer thus far, the promise of immunotherapy is eagerly being pursued. Do we need a chemotherapy backbone in the immunotherapy era? It remains to be seen whether the optimal use of checkpoint inhibitors in esophagogastric cancers will be as single agents, as combination immunotherapies, or in combination with conventional cytotoxic chemotherapy. Can incorporation of early palliative care in patients with esophageal and gastroesophageal cancers improve outcome? Despite encouraging data in patients with advanced lung cancer, early palliative care did not improve quality of life (QOL) at week 12 in a mix of patients with GI malignancies (25). Given the high symptom burden in patients with esophageal and GEJ cancer, however, additional studies should be conducted in this patient population. The impact of early palliative care is worth examining in coordination with our efforts to select an optimal therapeutic regimen and may have a significant impact on patients' tolerance of chemotherapy.

Have we advanced the science and care of esophageal cancer? Yes, but a lot of work remains. FOLFOX is a reasonable chemotherapy backbone for future clinical trials and the work of Enzinger and colleagues is commendable for helping to consolidate future research. While FOLFOX is a reasonable chemotherapy backbone, it is unlikely to shoulder the load of all future treatment trials in all subsets of advanced esophageal cancer.

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