Systemic therapy for esophageal cancer: chemotherapy

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Abstract: As one-half of patients with esophagogastric cancer (EGC) present with metastatic disease and the majority of patients with locally advanced disease will eventually develop metastatic disease despite multimodality therapy, most patients will receive palliative chemotherapy at some point. The reference first-line regimen consists of a fluoropyrimidine/platinum combination, which is the standard in East Asia, where this disease is endemic. Options include infusional 5-fluorouracil (5-FU), capecitabine, S-1 and other oral 5-FU pro-drugs and cisplatin or oxaliplatin. The addition of docetaxel to 5-FU/cisplatin is an option for young and fit patients, based on a phase III study, but is associated with significant hematologic toxicity and modest benefit. In the UK, epirubicin is added to the doublet, in the absence of phase III data suggesting a clear benefit; in fact, recent studies suggest no benefit. In the second- and third-line setting, taxanes and irinotecan are now validated options. Overall, improvements on the basis of chemotherapy have been marginal over the last 30 years and current efforts focus on targeted therapies and immunotherapy.

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Introduction

Approximately 50% of patients with a diagnosis of esophagogastric cancer (EGC) present with overt metastatic disease, and chemotherapy is the mainstay of palliation in this setting. With the high likelihood of the development of metastatic disease in patients with initial locoregional cancer, systemic chemotherapy is ultimately required in the majority of patients. This chapter focuses on the use of systemic chemotherapy in the treatment of advanced esophageal cancer.

Single-agent chemotherapy

Until the early 1990s, commonly used chemotherapy drugs to treat EGCs included 5-fluorouracil (5-FU) (1,2), cisplatin (3-5) and mitomycin (6-8), with single-agent response rates (RRs) ranging from 10% to 25%. Newer drugs with single-agent activity that have since been evaluated include the oral 5-FU pro-drugs [capecitabine (9,10) and S-1 (11-13)], the taxanes [paclitaxel (14-16) and docetaxel (17-19)] and irinotecan (20), with RRs of 15% to 45%.

A Cochrane meta-analysis by Wagner *et al.* that combined three trials of chemotherapy *vs.* best supportive care (BSC) revealed a clear survival benefit for treatment [hazard ratio (HR) 0.37, 95% confidence interval (CI): 0.24–0.55] (21). This translates into an improvement in median overall survival (OS) from 4.3 to 11 months with chemotherapy.

Given the modest activity of single agents in esophageal cancer, combination chemotherapy of two and even three drugs has been extensively studied. The Cochrane meta-analysis of 13 trials of 1,914 patients (which mostly evaluated older chemotherapy regimens) does show modest improvements in RRs (35% *vs.* 18%, odds ratio 2.91, 95% CI: 2.15–3.93), median time-to-progression (TTP) (5.6 *vs.* 3.6 months, HR 0.67; 95% CI: 0.49–0.93) and median OS (8.3 *vs.* 6.8 months, HR 0.82, 95% CI: 0.74–0.90) with combination over single-agent chemotherapy (21).

Despite incremental advances, the duration of response to both modern single agents and combination regimens is only generally 4 to 6 months, with median OS of 10 to 12 months.

Combination chemotherapy

Fluoropyrimidine/platinum doublet

The combination of infusional 5-FU/cisplatin has been studied extensively since the 1980s and the doublet of a fluoropyrimidine with a platinum compound remains a reference regimen in many contemporary trials. Of note, contemporary studies have generally enrolled patients with adenocarcinoma histology, irrespective of whether the tumor is found in the lower esophagus, gastroesophageal junction (GEJ) or stomach.

More contemporary trials have evaluated substitutions of both of these drugs with either an oral 5-FU pro-drug [capecitabine (22) or S-1 (23)] and/or the newer platinum compound oxaliplatin (22,24). Regimens such as S-1/cisplatin (23), capecitabine/cisplatin (25), infusional 5-FU/oxaliplatin (24) and capecitabine/oxaliplatin (along with the anthracycline epirubicin) (22) appear to have at least comparable efficacy compared to 5-FU/cisplatin and are also mostly associated with decreased toxicity and increased ease of administration. In fact, an individual patient data meta-analysis of two randomized trials that compared capecitabine-based with infusional 5-FU based regimens—the capecitabine/cisplatin *vs.* 5-FU/cisplatin trial (25) and the Randomized ECF for Advanced and Locally Advanced EGC 2 (REAL-2) study (22) mentioned above and discussed in more detail subsequently—suggested that capecitabine-based treatments are associated with superior RR and OS than infusional 5-FU regimens (26).

The other platinum analog—carboplatin—has been associated with low single-agent activity in esophagogastric adenocarcinomas (27). However, phase II trials of carboplatin combined with taxanes indicate promising activity (28,29) and the combination of carboplatin/paclitaxel with concurrent radiation has emerged as an international standard in locally advanced disease (30).

Although routinely used, one of the only studies that has shown a benefit for a fluoropyrimidine/doublet compared to a fluoropyrimidine alone is the phase III SPIRITS (S-1 Plus cisplatin versus S-1 In RCT In the treatment for Stomach cancer) study. S-1 is a mixture of tegafur (an oral 5-FU prodrug), gimeracil (a dihydropyrimidine dehydrogenate inhibitor that may potentiate the effect of 5-FU) and oteracil (which may reduce the gastrointestinal toxicity of 5-FU). In this Japanese trial, where 298 patients with advanced gastric cancer were randomized to receive S-1 with or without cisplatin, the doublet was associated with a higher RR (54% *vs.* 31%, P=0.002) and superior OS (13.0 *vs.* 11.0 months, P=0.04) (31). While this study helped to establish S-1/cisplatin as a standard therapy in Japan, the phase III FLAGS trial performed in U.S. and European patients comparing S-1/cisplatin *vs.* 5-FU/cisplatin failed to demonstrate superiority of S-1 over infusional 5-FU (23). As such, S-1 is not widely used outside of East Asia. This is also in part because S-1 appears to be associated with increased toxicities in Asian patients compared to those from the rest of the world (for example, the FLAGS study used a different dose/schedule of S-1 compared to that used in East Asia).

Moving beyond 5-FU/cisplatin

Despite the widespread use at the time of high dose cisplatin (100 mg/m^2) with a 4- or 5-day infusion of 5-FU (at 1,000 mg/m^2/day) as a standard therapy, two seminal trials in the late 1990s directed the development of chemotherapy regimens in EGC away from this schedule of therapy. A European trial compared 5-FU/cisplatin with the FAMTX (bolus 5-FU/doxorubicin/methotrexate) and ELF (etoposide/leucovorin/5-FU) regimens (32). All regimens performed poorly, with high rates of toxicity, RRs ≤20% and median OS of only approximately 7 months. These disappointing results led investigators in continental Europe to pursue better-tolerated colorectal cancer-like schedules of biweekly infusional 5-FU with a platinum compound (24) and to investigate taxane- and irinotecan-based chemotherapy.

The second key trial was performed in the UK and compared FAMTX to the ECF regimen, which combines epirubicin with a lower dose of cisplatin (60 mg/m^2) and a 21-day infusion of low dose 5-FU (200 mg/m^2/day) (33). The ECF arm achieved superior RRs (45% *vs.* 21%, P=0.0002), median OS (8.9 *vs.* 5.7 months, P=0.0009) and quality-of-life (QoL) at 24 weeks compared with FAMTX. This trial established ECF as the reference regimen in the UK.

Anthracyclines

Following the validation of the ECF regimen, a subsequent study compared it to the MCF regimen, where mitomycin was substituted for epirubicin (and the infusional 5-FU was administered at a higher dose of 300 mg/m^2/day) (34). While designed to test the superiority of MCF, the study reported no significant differences in RR or median survival but found that QoL was better maintained with ECF. As

such, ECF remained the preferred regimen, even as some investigators questioned if either of these triplet regimens is actually superior to the 5-FU/cisplatin doublet.

Subsequently, the REAL-2 study compared the ECF regimen to the ECX (which involves the substitution of 5-FU with capecitabine), the EOF (substitution of oxaliplatin for cisplatin) and the EOX regimens (a double substitution of both capecitabine and oxaliplatin) in patients with advanced esophagogastric adenocarcinomas or Squamous Cell Carcinomas (SCCs) (22). All the combinations had similar RRs (40% to 48%) and toxicities and the EOX regimen was associated with improved median OS compared to the ECF regimen (11.2 *vs.* 9.9 months, P=0.02), leading the authors to propose that EOX regimen could replace ECF in future trials.

Despite the standard use of ECF or one of its derivates in the UK, the clear superiority of this triplet over a fluoropyrimidine/platinum doublet has never been demonstrated in a randomized fashion. One piece of evidence frequently cited to support the incorporation of an anthracycline comes from the previously cited Cochrane meta-analysis, which analyzed three individually negative trials (including the negative evaluation of ECF *vs.* MCF described above) (21). Combining all three trials revealed a survival benefit for the addition of epirubicin (HR 0.77, 95% CI: 0.62–0.91), which translates into an approximate 3-month survival advantage. However, this conclusion comes largely from the comparison of ECF *vs.* MCF since that trial contributed two-thirds of the patients to the meta-analysis. Given the greater toxicity noted on the MCF arm and the fact that the comparison is not purely between a 5-FU/cisplatin-only arm at identical doses and ECF, a determination of the relative merits of adding epirubicin remains difficult to make.

Continuing questions regarding the benefit of an anthracycline were raised by the results of a randomized phase II trial performed by the U.S. Cancer and Leukemia Group B (CALGB) and Eastern Cooperative Oncology Group (ECOG). The CALGB 80403/ECOG 1206 trial randomized 245 patients (222 with adenocarcinomas) to one of three chemotherapy regimens—ECF, FOLFOX (biweekly bolus and infusional 5-FU/leucovorin/oxaliplatin) or cisplatin/irinotecan—along with cetuximab, a monoclonal antibody against the epidermal growth factor receptor, for patients with advanced esophagogastric adenocarcinomas or SCCs (35). In the patients with adenocarcinomas, both the ECF and FOLFOX regimens plus cetuximab produced RRs of >40% (61% and 54% respectively), which met the primary objective of the trial. However, survival outcomes were very similar between the cetuximab/ECF and cetuximab/FOFLOX arms. Median progression-free survival (PFS) was 7.1 *vs.* 6.8 months and median OS was 11.6 *vs.* 11.8 months respectively. Overall, cetuximab/FOLFOX appeared to be the least toxic of the three regimens.

Of course, the randomized phase II nature of this study was not designed to detect a survival difference between these regimens and the contribution of cetuximab, now thought to be either neutral or even detrimental, cannot be determined. Nevertheless, the results of this trial do support the contention that any benefit of an anthracycline, if there is any benefit at all, is likely to be small. Another notable finding of this study is that cetuximab/cisplatin/irinotecan had the lowest RRs and survival outcomes and the highest toxicity rates, which has contributed to a significant decline in the use of this chemotherapy regimen in the first-line setting. Correspondingly, the favorable toxicity profile and activity of the FOLFOX arm has reinforced its established role as the standard first-line regimen in the US.

The lack of data to support adding an anthracycline to a doublet regimen in the metastatic setting mirrors data in the locally advanced setting. The OEO-5 study performed in the UK showed no survival benefit for such a three-drug regimen compared to 5-FU/cisplatin (36).

Taxanes

In comparison to the unclear benefit of adding an anthracycline to a fluoropyrimidine/platinum doublet, there are randomized data to support the addition of a taxane. The phase III V325 randomized trial in GEJ and gastric adenocarcinomas compared the DCF regimen (docetaxel/cisplatin/infusional 5-FU) to infusional 5-FU/cisplatin (37). The addition of docetaxel improved RRs (37% *vs.* 25%, P=0.01) and TTP (5.6 *vs.* 3.7 months, P<0.001) but OS was only slightly improved (median OS 9.2 *vs.* 8.6 months, 2-year OS 18% *vs.* 9%, P=0.02). In addition, the three-drug regimen was associated with significantly more toxicity, including a grade 3/4 neutropenia rate of 82% (*vs.* 57%) and febrile neutropenia in 29% of patients (*vs.* 12%). Fifty percent of patients came off treatment either due to severe adverse events or consent withdrawal. Despite these significant toxicities, the authors reported a slower decrement in QoL measurements in the DCF arm (38). On the basis of this study, docetaxel was approved by the U.S. Food and Drug Administration (FDA) in 2006 for use with

5-FU/cisplatin in this context.

As the toxicities seen with the parent DCF regimen are significant and may outweigh its small survival advantage over 5-FU/cisplatin, it has not been widely adopted. It is also unclear if similar survival benefits would be accrued by the sequential use of first-line 5-FU/cisplatin followed by subsequent docetaxel (or paclitaxel) at progression.

Several investigators have attempted to modify the regimen to increase tolerability. For example, our group performed a randomized phase II trial of parent DCF (with prophylactic growth factor support) *vs.* a modified DCF (mDCF) regimen (consisting of reduced doses of docetaxel and cisplatin administered with bolus and 2-day infusional 5-FU and leucovorin every 14 days) (39). mDCF was associated with decreased toxicity compared to parent DCF (neutropenic fever rate 9% *vs.* 16% and grade 3/4 nausea/vomiting rate 2% *vs.* 23%), while median OS appeared superior in the mDCF arm (18.8 *vs.* 12.6 months, P=0.007). Nevertheless, 22% of the patients (who had a median age of 59 years) receiving mDCF required hospitalization in the first three months, mostly for treatment-related toxicities (febrile neutropenia and gastrointestinal toxicities), reinforcing the notion that this remains a relatively difficult regimen to administer and is an option only for healthy, motivated patients with frequent access to medical evaluation.

Another extensively-evaluated and commonly-used modification is the German FLOT regimen, which consists of the substitution of oxaliplatin for cisplatin and is built around a 1-day infusion of 5-FU every 14 days. Encouraging activity was noted in a phase II study of 59 patients, which reported a response rate of 58% and a median OS of 11.1 months (40). The FLOT regimen was subsequently compared to the 5-FU/oxaliplatin doublet (FLO) in the randomized phase II FLOT65+ study, which enrolled patients who were ≥65 years old with either locally advanced or metastatic diseases (41). No benefit was seen for the triplet combination in patients ≥65 years old with metastatic disease and in any patient ≥70 years old. This study again emphasizes the need for strict patient selection for such three-drug regimens.

Of note, the FLOT regimen was recently shown to be superior to ECF/ECX in the peri-operative setting for GEJ/gastric adenocarcinomas. A new standard-of-care was recently established by the presentation of the German FLOT4 study in abstract form (42). This study compared peri-operative ECF/ECX *vs.* FLOT chemotherapy. FLOT improved OS from a median of 35 to 50 months (HR 0.77, P=0.012). The 3-year OS rate was 48% with ECF/ECX and 57% with FLOT. PFS was also superior with FLOT (30 *vs.* 18 months, HR 0.75, P=0.004).

Yet another slight variant of parent DCF (termed TCF, employing a 14-day 5-FU infusion every 21 days) was compared to the ECF regimen in a Swiss phase II randomized trial of advanced gastric cancer patients (43). TCF was associated with a superior RR (the primary endpoint) when compared to ECF (37% *vs.* 25%) but the toxicity—particularly rates of neutropenia and neutropenic fever—was again substantial.

Other groups have substituted the cisplatin and the infusional 5-FU in DCF. The randomized phase II GATE study compared docetaxel/oxaliplatin (TE) alone or with 2-day infusional 5-FU (F) or capecitabine (X) found superior outcomes and toxicity for the TEF arm (44). Notably, the febrile neutropenia rate in the TEF arm was only 2% and median OS was an encouraging 14.6 months.

In addition, docetaxel doublets have also been evaluated. The Swiss trial above of TCF *vs.* ECF also included a third arm with docetaxel/cisplatin (TC). Activity and survival were comparable between the TC and TCF arms and there was a suggestion of superior toxicity profile for the two-drug TC regimen compared to the three-drug TCF regimen. A phase III study did also compare docetaxel/cisplatin to infusional 5-FU/leucovorin/cisplatin. While it has only been reported in abstract form and the results have never been published, there were not any significant differences in outcomes between both treatment groups (45).

Similarly, another randomized phase II study demonstrated comparable activity for a regimen of DF (docetaxel/5-FU) *vs.* ECF in advanced gastric cancer patients, although the study was not powered for a head-to-head comparison of both regimens (46). Single-arm phase II studies of docetaxel/capecitabine have also suggested similar activity and toxicity compared to docetaxel/5-FU (47,48).

Overall, these results suggest that docetaxel-based regimens are superior only when combined with a fluoropyrimidine and platinum compound. While the question has not been rigorously addressed, docetaxel doublets do not appear to be superior to 5-FU/cisplatin (with or without an anthracycline).

In addition to docetaxel, other investigators have combined cisplatin with paclitaxel, both with and without 5-FU in phase II evaluations (49-52). RRs ranged from 43% to 50% but toxicity included significant diarrhea, neurotoxicity and myelosuppression.

Finally, several novel taxane derivatives have been

evaluated. Tesetaxel, an oral taxane derivative, was evaluated in 36 patients as second-line therapy following progression on a fluoropyrimidine/platinum doublet in three different doses (53). The median OS was 7.8 and 7.5 months in two cohorts, while the follow-up was too short in the third cohort. These data were presented in abstract form in 2012 and have never been published. There do not appear to be any active clinical studies evaluating this drug in EGC.

More recently, nanoparticle albumin-bound (nab)-paclitaxel was compared to paclitaxel as second-line therapy in a phase III non-inferiority study that randomized 741 Japanese patients to two schedules of nab-paclitaxel (q1 *vs.* q3 week) *vs.* weekly paclitaxel (54). Median OS was 10.3, 11.1 and 10.9 months respectively. Weekly nab-paclitaxel was found to be non-inferior to weekly paclitaxel (HR 0.97, 97.5% CI: 0.76–1.23, P=0.0085), whereas q3 week nab-paclitaxel was not non-inferior to weekly paclitaxel (HR 1.06, 97.5% CI: 0.87–1.31, P=0.062). QoL was similar between both groups.

Taken together, these data would suggest that novel taxanes are not likely to provide meaningful benefit over paclitaxel or docetaxel. This is especially true of nab-paclitaxel, which is significantly more expensive than paclitaxel and appears to offer no particular advantage.

Irinotecan

Irinotecan is another active agent in EGCs that has been combined with mitomycin, 5-FU/leucovorin and cisplatin with or without docetaxel in phase II evaluations, with RRs ranging from 30% to 65% (55-62). Toxicities on some of these trials, e.g., with cisplatin/docetaxel/irinotecan, have been substantial.

A randomized phase II trial compared the FUFIRI regimen (weekly infusional 5-FU/leucovorin/irinotecan) with cisplatin/irinotecan in patients with advanced GEJ and gastric adenocarcinomas (57). FUFIRI was associated with superior outcomes and less neutropenia than cisplatin/irinotecan. This led to a subsequent phase III trial of FUFIRI *vs.* 5-FU/cisplatin. Both regimens had comparable efficacy but there was less neutropenic fever and grade 3/4 stomatitis and nausea in the FUFIRI arm (63). Only the incidence of grade 3/4 diarrhea was increased in the FUFIRI arm, although more patients withdrew from the 5-FU/cisplatin arm than the FUFIRI arm (22% *vs.* 10%, P=0.004) for drug-related adverse events. Although there was no clear benefit for FUFIRI over 5-FU/cisplatin, the favorable toxicity of this combination supports its use as a front-line option, especially in patients who are not candidates for a platinum compound.

The use of first-line 5-FU/irinotecan is now further supported by the results of a phase III French FFCD group, which randomized 416 patients to the FOLFIRI regimen (biweekly bolus and infusional 5-FU/leucovorin/irinotecan) *vs.* ECX in patients with advanced gastric cancer (64). At progression, patients received therapy with the alternate regimen. This study revealed a superior time-to-treatment failure for FOLFIRI *vs.* ECX (5.1 *vs.* 4.2 months, P=0.008) and comparable PFS (5.3 *vs.* 5.8 months, P=0.96) and OS (9.5 *vs.* 9.7 months, P=0.95). Toxicities were significantly less for FOLFIRI, e.g., overall grade 3/4 toxicity rare of 69% *vs.* 84%, P<0.001. Time-to-treatment failure was selected as the primary endpoint as it captured discontinuation of a regimen for both efficacy and toxicity reasons.

Finally, Boku *et al.* also performed a phase III trial that randomized Japanese patients to infusional 5-FU *vs.* cisplatin/irinotecan (a third arm was designed to evaluate and did confirm non-inferiority of S-1 *vs.* infusional 5-FU) (11). When compared to infusional 5-FU, cisplatin/irinotecan was associated with an improved RR (38% *vs.* 9%) but only a non-significant trend toward improved median OS (12.3 *vs.* 10.8 months, P=0.055), at the expense of significantly more grade 3/4 toxicities. As noted above, results of the CALGB 80403/ECOG 1206 study which randomized patients to cetuximab plus ECF *vs.* FOLFOX *vs.* cisplatin/irinotecan revealed that the cisplatin/irinotecan arm had the lowest RR and shortest median OS (35).

Taken together, these results have led many oncologists to move away from using cisplatin/irinotecan as a first-line regimen for advanced EGCs, although FOLFIRI has recently emerged as a viable first-line option. Some uncertainty about the superiority of irinotecan in the first-line setting is reinforced by the Cochrane meta-analysis of four clinical trials, which reveals a non-statistically significant trend toward a small survival benefit for an irinotecan-containing regimen (HR 0.86, 95% CI: 0.73–1.02) (21). Notably, the recent FFCD study of FOLFIRI discussed above was not included in this meta-analysis.

Second-line chemotherapy

Until relatively recently, there were no large randomized studies to support a survival benefit for second-line chemotherapy in EGCs. There are now three randomized studies performed in patients with gastric cancer to support such a benefit.

The first study of 202 Korean patients with an ECOG performance status of ≤1 who had previously received ≤2 prior regimens were randomized in a 2:1 ratio to further treatment with either docetaxel or irinotecan *vs.* BSC (65). The patients who received chemotherapy had a superior OS (5.3 *vs.* 3.8 months; HR 0.66, P=0.007) and therapy was well-tolerated, with manageable hematologic toxicities and comparable rates of non-hematologic toxicities in both groups. There were no significant differences between either chemotherapy arm.

The Japanese WJOG 4007 study then randomized 223 patients to second-line paclitaxel *vs.* irinotecan (66). Median OS was comparable (9.5 *vs.* 8.4 months, P=0.38), although there appeared to be less toxicity in the paclitaxel arm and more of those patients went on to receive third-line chemotherapy than in the irinotecan-arm. Finally, the UK COUGAR-2 study confirmed the benefit for second-line docetaxel *vs.* BSC in a Western population, with a median OS of 5.2 *vs.* 3.6 months (P=0.01) (67).

Based on these results, patients with good performance statuses should be offered additional non-cross resistant treatment beyond progression on first-line chemotherapy. As noted in a separate chapter, the combination of paclitaxel with ramucirumab, an antibody against vascular endothelial growth factor receptor 2 (VEGFR-2) is now considered the standard-of-care in the second-line setting (68).

Response rates in adenocarcinoma and SCC

Generally, it appears that adenocarcinoma and SCC tumors have overlapping RRs to combination chemotherapy, similar to the experience with non-small cell lung cancer. Few single agents have been tested in both cell types, and the number of patients treated in such studies has been small. Phase III studies in SCC patients are also lacking. As such, regimens that are active in adenocarcinoma histology are routinely extrapolated and used to treat patients with SCC tumors.

Biomarkers

Given the modest benefit of chemotherapy, efforts have focused on biomarkers that may predict response to chemotherapy. For example, the Southwestern Oncology Group prospectively evaluated the association of excision repair cross-complementing 1 (ERCC1) and thymidylate synthase (TS) mRNA levels in 91 patients with esophageal cancer who were treated with 5-FU and oxaliplatin and radiation followed by surgery (69). ERCC1 is the rate-limiting step in the nucleotide excision repair pathway and is thought to be important in repairing DNA damage induced by platinum chemotherapy; low ERCC1 expression levels have been associated with improved outcomes to platinum-based therapy in gastric cancer (70). Similarly, low expression levels of TS, which is the main target for 5-FU inhibition, have also been associated with improved outcomes for patients with gastric cancer treated with 5-FU-based regimens (71).

In this study, higher ERCC1 mRNA levels were associated with worse PFS, although TS levels did not correlate with PFS or pathological complete response (pCR) rate. Because all patients received the same treatment, it is not possible to determine whether ERCC1 expression is merely prognostic or actually predictive of benefit from chemoradiation with this regimen.

Unfortunately, the only randomized evaluation of ERCC1 as a predictive marker was recently reported in abstract and failed to show a benefit for its use (72). In this study, 203 patients with esophagogastric adenocarcinoma were randomized to receive either FOLFOX or irinotecan/docetaxel and outcomes were analyzed by low *vs.* high ERCC1 levels. In all patients, FOLFOX was associated with a higher RR (41% *vs.* 27%, P=0.05) and PFS (5.7 *vs.* 2.9 months, HR 0.70, P=0.01) and a trend toward improved OS (11.4 *vs.* 8.7 months, HR 0.82, P=0.19). There was no difference in outcomes by ERCC1 levels.

Conclusions

The development of chemotherapy combinations over the last 20 years appears to have plateaued in terms of activity and tolerability. While two-drug regimens remain the standard and are generally tolerated by the majority of patients, three-drug regimens of docetaxel with a fluoropyrimidine and platinum drug are an option for healthy and motivated patients. Our opinion is that there is no role for the anthracycline epirubicin in either the metastatic or peri-operative setting.

In general, ongoing research efforts have shifted from the evaluation of novel chemotherapy drugs and regimens to the incorporation of targeted agents and immunotherapy approaches, as discussed elsewhere in this review.

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Footnote

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