

# REVIEWING THE ROLE OF CYTOTOXICS IN OESOPHAGOGASTRIC CANCER IN THE REFRACTORY RELAPSED AND ADVANCED SETTINGS

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## Abstract

Advanced oesophagogastric cancer is an incurable disease and leading cause of cancer-specific mortality. Despite some progress in recent years, its management poses a challenge due to increasing incidence, geographical variation, histologic heterogeneity, biologic behaviour and lack of consensus on standard chemotherapy with or without biologic agents. The purpose of this review is to discuss the current controversies in selection of chemotherapy regimens. The review involves analysis of recent clinical trials to discuss the impact and implications of their results on the management of advanced oesophagogastric cancer and the planning of the next generation of clinical trials.

Small but significant improvements in survival for oesophagogastric cancer have occurred over last three decades with the five-year survival of oesophageal cancer improving from 5% to 17% and stomach cancer from 16% to 28%.<sup>1</sup> According to Australian Institute of Health and Welfare, there were a total of 3400 new stomach and oesophageal cancer cases and 2400 deaths.<sup>1</sup>

Nearly 50% of patients with a diagnosis of oesophagogastric cancer present with overt metastatic disease, and chemotherapy is the mainstay of palliative treatment. While data from clinical trials before the 1990s were largely ineffective due to the use of single-agent chemotherapies in heterogeneous, small patient populations, more recent trials with combination chemotherapy, targeted agents, and neoadjuvant chemotherapy are more promising. With the increasing use of chemotherapy as an adjunct to surgical management, systemic chemotherapy will ultimately be used to treat the majority of patients with oesophagogastric cancer.

## Basis of chemotherapy

In patients with advanced oesophagogastric cancer, chemotherapy clearly improves survival and quality of life compared with best supportive care alone, although the evidence is more compelling in gastric cancer specifically.<sup>2-5</sup> In a meta-analysis of 35 trials with a total 5726 patients with advanced gastric cancer, systemic chemotherapy was compared with best supportive care. The main finding of this analysis was that patients undergoing chemotherapy lived for an average of six months longer than those receiving best supportive care [hazard ratio (HR) 0.37, 95% confidence intervals (CI) 0.24 to 0.55].<sup>6</sup> Furthermore, combination chemotherapy had better survival than single-agent chemotherapy (HR 0.82; 95% CI 0.74 to 0.90). However, this benefit was at the expense of increased toxicity. Therefore, in the absence of contraindications and concerns over toxicity, combination chemotherapy would be used as initial treatment in patients with good performance status.

In contrast, oesophageal cancer is more heterogeneous and evidence supporting chemotherapy alone is less compelling. The grouping of locally advanced and metastatic disease with different pathologies (ie. squamous and adenocarcinoma) makes interpretation of results difficult. Furthermore, radiotherapy is often added for local control. A multicentre randomised French study currently accruing patients with only metastatic squamous cell oesophageal carcinoma may help to ascertain if there is a benefit of chemotherapy over best supportive care.<sup>7</sup> Similarly, Trans-Tasman Radiation Oncology Group (TROG) is conducting a randomised phase III study in advanced oesophageal carcinoma to compare palliative benefit in dysphagia in patients treated with radiotherapy versus chemo-radiotherapy (TROG 03.01 study).<sup>8</sup>

## Current options of CF versus ECF versus DCF

### Oesophageal cancer

Cisplatin and 5-Fluorouracil (5-FU) both have single agent activity in oesophagogastric cancer.<sup>9</sup> The use of the combination of cisplatin and 5-FU (CF) for the treatment of oesophageal cancer was primarily inspired by the activity of this regimen in squamous cell carcinoma of the head and neck. Cisplatin (100 mg/m<sup>2</sup>) as a single agent and cisplatin with 5-FU (1000 mg/m<sup>2</sup> by continuous intravenous infusion on days 1-5) were compared in a randomised study of 88 patients with metastatic squamous cell carcinoma of the oesophagus.<sup>10</sup> This study confirmed the superior efficacy (response rate 19% v 35%, medium duration of response 28 v 33 weeks) of combination treatment over single agents at the expense of greater toxicity. Response rates to cisplatin and 5-FU are supported in other trials with response rates ranging from 35% to 40%.<sup>11,12</sup> Efforts have been made to improve upon this regimen by adding other agents but with no real progress and the true role of palliative chemotherapy remains controversial.

### **Gastric cancer (including gastro-oesophageal junction)**

The combination of epirubicin, cisplatin and 5-fluorouracil (ECF) was developed in the 1990s and remains the most popular regimen in Australia for advanced gastric and oesophagogastric cancer. In a pivotal Phase III trial, 274 patients were randomised to receive either ECF or Adriamycin, and high-dose 5-fluorouracil and methotrexate (FAMTX). ECF demonstrated a response rate of 45% compared with 21% for FAMTX, and a median survival of 8.9 versus 5.7 months ( $p = 0.0002$ ).<sup>14</sup> The main drawback of the regimen was the requirement of central venous access for protracted venous infusion of 5-FU. The pro-coagulant properties of the cancer and the central line led to its removal in 19% of trial patients. Toxicities were broadly comparable except that ECF caused more alopecia, nausea and vomiting, but less neutropaenia and infection.

There remains some question as to the benefit of adding an anthracycline to CF. The addition of an anthracycline to cisplatin and 5-FU has shown a trend towards benefit in three randomised phase III plus two small phase II trials. Data from these trials were pooled in a meta-analysis that reported a statistically significant benefit in favour of anthracycline/platinum-containing regimens.<sup>15</sup> The survival benefit was estimated to afford an additional two months and, of the available agents, epirubicin appeared to be the best tolerated. The meta-analysis was criticised for the small numbers of patients and for including a study that didn't address the issue of doublet versus triplet combination, but compared epirubicin with mitomycin C (M) in a triplet regimen (mitomycin C, cisplatin, and 5-FU v ECF).<sup>15</sup> An additional but unpublished meta-analysis by Group GASTRIC has suggested no additional benefit of an anthracycline.<sup>16</sup> Therefore, it is still unclear whether ECF is more effective than doublet chemotherapy in advanced oesophagogastric cancer. Furthermore, toxicity is more severe with triplet than doublet chemotherapy. ECF, or a variation of it, is still considered to be a standard regimen in Australia and Europe based on these data.

The addition of docetaxel as a third agent added to CF in a phase III trial of gastroesophageal junction and gastric cancer has been reported. The 5-FU was dosed at 1000 mg/m<sup>2</sup> by continuous infusion over five days combined with cisplatin 100 mg/m<sup>2</sup>, compared to cisplatin 75 mg/m<sup>2</sup>, 5-FU 750 mg/m<sup>2</sup> by continuous infusion over five days, and docetaxel 75 mg/m<sup>2</sup> (DCF) in 445 patients with metastatic gastric or gastroesophageal junction adenocarcinoma.<sup>21</sup> The DCF regimen resulted in a higher response rate and longer time to progression (36% and 5.6 months, respectively) compared to 5-FU and cisplatin (26% and 3.7 months), but only a marginal median survival improvement of 0.6 months was noted. Toxicity was substantial in both treatment arms, including haematologic and gastrointestinal toxicity, with 82% of patients receiving the three-drug combination experiencing grade 3 or 4 neutropaenia. The potential superiority of DCF was underscored by a recent randomised phase II trial comparing ECF to DCF in gastric and gastroesophageal junction cancer.<sup>22</sup> The DCF regimen appeared to result in

a superior response rate and time to tumour progression when compared to ECF, but toxicity, particularly rates of neutropaenia and neutropaenic fever, were substantial. The high rate of haematological toxicity has limited the regimen's use outside of American institutions. Currently in Australia, the ATTAX-3 trial is attempting to address this issue among others. It uses weekly docetaxel to reduce myelosuppression, combining it with cisplatin and 5-FU (or capecitabine – an oral prodrug of 5-FU) and then randomised to panitumumab versus placebo.<sup>23</sup> The ATTAX-3 trial is actively recruiting.

Although triplet therapy (ECF or DCF) is used by many, the toxicity trade-off does mean that CF is still used as an alternate option by many clinicians. Thus attempts to improve doublet regimens are still relevant. The combination of irinotecan and infusional 5-FU was compared head to head to conventional 5-FU and cisplatin in a recent phase III trial in gastric and gastroesophageal junction cancers.<sup>26</sup> Irinotecan 80 mg/m<sup>2</sup> in combination with 5-FU 2 g/m<sup>2</sup> over a 24-hour infusion, and leucovorin 500 mg/m<sup>2</sup> administered weekly for six weeks on and one week off, was compared to cisplatin 100 mg/m<sup>2</sup> and 5-FU 1000 mg/m<sup>2</sup> continuous infusion for five days every four weeks in 333 patients. There was no difference in response rate (26% v 32%), time to progression (4.2 v 5.0 months), or median survival (8.7 v 9.0 months). However, the toxicity profile significantly favoured the irinotecan/5-FU combination, with less neutropaenia, neutropaenic fever, stomatitis and nausea. Only the rate of grade 3 or 4 diarrhoea was greater in the irinotecan arm. This trial suggests that irinotecan/5-FU may represent a comparably active but better-tolerated alternative to 5-FU/cisplatin.

### **Substitution of capecitabine and oxaliplatin in triplet and doublet regimens**

Capecitabine (X) and oxaliplatin represent agents that are potential substitutes for infusion fluorouracil or cisplatin respectively. The largest clinical trial in the management of locally advanced or metastatic oesophagogastric cancer was a two-by-two design, REAL-2 trial, in which 1002 patients were randomly assigned to receive triplet therapy with epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).<sup>27</sup> The primary endpoint was non-inferiority in overall survival for the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin. For the capecitabine–fluorouracil comparison, the hazard ratio for death in the CX group was 0.86 (95% CI, 0.80 to 0.99); for the oxaliplatin–cisplatin comparison, the hazard ratio for the oxaliplatin group was 0.92 (95% CI, 0.80 to 1.10). The upper limit of the confidence intervals for both hazard ratios excluded the predefined non-inferiority margin of 1.23. Median survival times in the ECF, ECX, EOF and EOX groups were 9.9 months, 9.9 months, 9.3 months and 11.2 months, respectively; and survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. In the secondary analysis, overall survival was longer with EOX than with ECF, with a hazard ratio for death of 0.80 in the EOX group (95% CI, 0.66 to 0.97;  $p$

= 0.02). Progression-free survival and response rates did not differ significantly among the regimens. Toxic effects of capecitabine and 5-FU were similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropaenia, alopecia, renal toxicity and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhoea and neuropathy.

Similar observations were made in a randomised, open-label, phase III Korean study, in which 316 patients were randomised to receive cisplatin with either Xeloda (CX) or protracted 5-FU (CF) to confirm noninferiority of CX versus CF for progression-free survival.<sup>28</sup> In the per-protocol population, median progression-free survival for CX (n = 139) versus CF (n = 137) was 5.6 versus 5.0 months with an unadjusted HR of 0.81 [95% CI 0.63–1.04, p < 0.001 versus non-inferiority margin of 1.25]. Median overall survival was 10.5 versus 9.3 months for CX versus CF (unadjusted HR = 0.85, 95% CI 0.64–1.13, p = 0.008 versus noninferiority margin of 1.25). There was no difference in treatment-related grade 3/4 adverse events in CX versus CF.

The combined data from REAL-2 and ML17032, which individually demonstrated that capecitabine is non-inferior to 5-FU, has shown a modest, but statistically significant benefit in overall survival in favour of the oral fluoropyrimidine, which was maintained on multivariate analysis.<sup>29</sup> When comparing the ECX arm in the REAL-2 study with the capecitabine and cisplatin arm in the ML17032 study, grade 3 and 4 neutropaenia were significantly higher in the triplet combination (51% v 16%) highlighting the importance of patient selection when considering doublet versus triplet chemotherapy.

### Impact of biological results on chemotherapy regimen

Finally, HER-2 positivity in metastatic gastric cancer may influence the choice of chemotherapy given the positive results of the ToGA trial, where overall survival was improved from 11.1 months with CF/X to 13.8 months with Herceptin plus CF/CX (HR 0.74, 95% CI 0.6–0.91; p=0.0046).<sup>30</sup> We have already discussed the controversy regarding the addition of an anthracycline and although some now consider CF/CX an acceptable backbone, the EOX arm of REAL-2 trial did have a high overall survival. One logical step is combining EOX with trastuzumab. Experience from breast cancer trials however, raises the potential of high cardiotoxicity from an anthracycline combination. The dilemma may be the selection of either trastuzumab or epirubicin. The relative benefit of the addition of trastuzumab or epirubicin to cisplatin plus fluoropyrimidine is unknown, although the benefit appears to slightly favour trastuzumab (4.2 months survival gain for trastuzumab in highly HER 2 positive patient in ToGA versus 2.0 months survival gain for epirubicin in the meta-analysis) and the toxicity profile is different.

### Second line options

Data from two recent randomised phase III trials suggest that there is definite but small survival advantage from second line chemotherapy in advanced gastric cancer. Park and colleagues conducted randomised phase III Korean

trials comparing second-line chemotherapy (docetaxel or irinotecan) plus best supportive care, versus best supportive care alone in patients with previously treated advanced gastric adenocarcinoma.<sup>32</sup> The addition of second-line chemotherapy to best supportive care was associated with a significant prolongation of overall survival relative to best supportive care alone (median overall survival was 5.1 months v 3.8 months) indicating a 37% reduction in the risk of death. The incidence of grade 3/4 adverse events was generally similar between treatment arms. These data confirm a previous phase III German trial that was discontinued early as a result of poor accrual, but which clearly demonstrated that patients with advanced gastric cancer benefited from second-line therapy if they had good performance status and were willing to undergo a second-line approach.<sup>33</sup> Table 1 summarises the results of potential second line options.

### Options after adjuvant chemotherapy

Recently, adjuvant chemotherapy has become a standard practice in T3 and/or node-positive gastric cancer after curative resection. Unfortunately, the majority of these patients will present with systemic disease in their follow-up. Rechallenge with cisplatin/ 5-FU if they relapsed >3 months after completing initial chemotherapy is one option addressed in a recent retrospective analysis. One hundred and six patients with oesophagogastric cancer were rechallenged with PF-based chemotherapy. The median progression-free survival and overall survival was 5.1 and 10 months respectively, for patients treated with radical intent previously.<sup>35</sup> This study demonstrated that selected patients with oesophagogastric cancer who relapse or progress >3 months after initial treatment with PF +/- epirubicin may benefit from re-introduction of PF-based chemotherapy. Similarly, in a smaller phase II study, 29 patients with oesophagogastric cancer were treated with capecitabine and irinotecan as second-line treatment after progressing on, or within three months of, platinum-based chemotherapy.<sup>36</sup> This study suggests that capecitabine and irinotecan has anti-tumour activity as second-line treatment for relapsed oesophagogastric cancer, and provides an important improvement in disease related symptoms. The second line options noted above could also be considered, in particular if relapse is within three months of adjuvant therapy. With increased perioperative ECF use, there is a need to design trials with new regimens and newer targeted drugs to give clinicians further options for this patient group.

### Conclusion

The majority of patients with oesophageal or gastric cancer will require palliative treatment at some point in the course of their disease. Cytotoxic chemotherapy can provide symptom palliation, improve quality of life and prolong survival in patients with advanced gastric cancer (including gastro-oesophageal junction), and potentially advanced oesophageal cancer although the evidence is not as robust. Despite a large number of randomised trials, there is no definite consensus as to the best agent or regimen. In general, combination chemotherapy regimens provide higher response rates than do single agents, but this translates into only modestly longer durations of disease control and survival that are measured in weeks to a few months. ECF and DCF

**Table 1:** Second line options after first line and after adjuvant chemotherapy failure.

Name of trial	Patient number	Treatment arms	Response rates	Survival	Gr 3-4 toxicities		
					N	D	HFS
Korean Trial <sup>32</sup>	243	Docetaxel or Irinotecan + BSC Versus BSC alone	- -	5.1 months Versus 3.8 months (P=.009) (HR – 0.63;95 % CI 0.47-0.86)	- -	- -	- -
AIO Study <sup>33</sup>	41	Irinotecan versus BSC	58% SD versus -	4 months versus 2.4 months (p=0.023) (HR=0.48; 95% CI 0.25-0.92)	10 % 0	20% 0	- -
PEP02 study <sup>34</sup>	135	Nano-Irinotecan versus Irinotecan versus Docetaxel	13.6% versus 6.8% versus 15.9%	- - -	9.1 % 13.6% 15.9%	27.3% 18.2% 2.3%	0% 6.8% 18.2%
RMH study <sup>35</sup> (retrospective)	106	Cisplatin +FU±E	-	Progression-free survival 5.1 months Overall survival 10 months	31 %	15%	-
RMH study <sup>36</sup> (phaseII)	29	Capecitabine+ Irinotecan	17%	Progression-free survival 3.1months (95% CI 2.2 – 4.1 months) Overall survival 6.5 months (95%CI 6-7.1 months)	-	-	-

*Key:*  
AIO - Arbeitsgemeinschaft Internistische Onkologie

*SD - Stable disease*  
*BSC - best supportive care*

combinations have emerged as standard regimens for first-line treatment. A major problem with these regimens is the need for central venous access and an ambulatory infusion pump and toxicity of the third agent. Data from the REAL-2 trial suggest that outcomes are comparable if capecitabine is substituted for infusional 5-FU, and when oxaliplatin is substituted for cisplatin in the ECF regimen. The addition of a biological agent has led to a review of CF/CX as an appropriate chemotherapy backbone partly based on better tolerance, although thus far only the addition of trastuzumab has been shown to lead to a survival advantage. Importantly, there is mounting evidence that second line chemotherapy improves survival and as was seen in colorectal cancer, improvements in subsequent therapy options are likely to finally see the survival of advanced oesophagogastric cancer continue to improve. The future is likely to focus on improved targeted agents added to chemotherapy in both first and second line treatment; and some of these options are summarised in table 2.

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**Table 2:** Ongoing and future trials.

Trial name	Type	Eligibility	Treatment arms	Endpoints	Status
ATTAX-3 <sup>23</sup>	Phase II	advanced oesophago-gastric cancer	chemotherapy only (wTCF/X) chemotherapy plus panitumumab	objective tumour response rate	recruiting
LOGiC	Phase III	HER 2 positive advanced gastro-oesophageal cancer	CapOx v Capox+ Lapatinib	progression-free survival overall survival	recruiting
REAL-3	Phase III	previously untreated advanced oesophago-gastric cancer	epirubicin, oxaliplatin and capecitabine (EOX) ±Panitumumab	progression-free survival	recruiting
OXFORD-COG study	Phase III	recurrent oesophageal cancer after failure of 1st line chemotherapy	gefitinib v placebo	overall survival	recruiting
XP-Simvastatin study	Phase III	advanced gastric cancer	capecitabine+ cisplatin+ simvastatin	response rate progression-free survival overall survival	recruiting
PALIC-C study	Phase III	advanced gastro-oesophageal cancer	paclitaxel plus capecitabine with capecitabine maintenance	response rate survival	approved
RAD 001 study	Phase III	gastric carcinoma after prior chemotherapy	paclitaxel with and without RAD001	progression-free survival	not active

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