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Is oxaliplatin the optimal platinum agent in gastric cancer?

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Abstract

Epirubicin–cisplatin–5-fluorouracil (ECF) is commonly used to treat advanced gastric cancer. Two new cytotoxic agents: the platinum, oxaliplatin, and the oral fluoropyrimidine, capecitabine, have the potential to replace the cisplatin and 5-fluorouracil (5-FU) components of ECF, respectively. Oxaliplatin showed anti-tumour activity in human gastric cancer cell lines and was active in Phase II studies in advanced gastric cancer. Using ECF as a reference regimen, the Phase III REAL-2 study compared oxaliplatin with cisplatin, and capecitabine with 5-FU in patients with previously untreated, locally advanced or metastatic cancer of the oesophagus, gastro-oesophageal junction or stomach. The results of this study indicate that oxaliplatin and capecitabine could replace the platinum and fluoropyrimidine components of ECF, with no adverse effect on efficacy, improved convenience and favourable safety. Further trials of oxaliplatin in combination with other cytotoxics may result in novel active regimens in this disease.

Keywords: Chemotherapy; Oxaliplatin; Platinum; Gastric cancer

1. Introduction

Although there has been a lack of consensus regarding the optimal chemotherapy for advanced gastric cancer, platinum–fluoropyrimidine doublets provide the core of many chemotherapy regimens. Epirubicin–cisplatin–5-fluorouracil (5-FU) [ECF] is widely used in the UK and Europe for the treatment of advanced gastro-oesophageal cancers, having demonstrated superiority to both 5-FU–doxorubicin–methotrexate (FAMTX) [1,2] and mitomycin–cisplatin–5-FU (MCF) [3] in patients with previously untreated advanced disease. In two randomized Phase III studies [1–3], ECF demonstrated overall response rates of 46% and 42%, median overall survival (OS) durations of 8.7 months and 9.4 months, and 1-year survival rates of 36% and 40%. A recent Cochrane meta-analysis substantiated the survival benefit of adding an anthracycline to cisplatin–5-FU (CF) in advanced gastric cancer: There was a 23% risk reduction (Hazard ratio [HR] 0.77; 95% confidence interval [CI], 0.62–0.95) for CF regimens including an anthracycline compared to those without [4].

Oxaliplatin (Eloxatin®) is a platinum compound that is complexed to a diaminocyclohexane carrier ligand. Like other platinum compounds, oxaliplatin stimulates apoptosis and ultimately cell death by forming adducts between two adjacent guanine or guanine adenine DNA base pairs – thereby inhibiting DNA replication and repair [5]. In terms of efficacy and toxicity, however, oxaliplatin is notably different from other platinum compounds. The platinum DNA adducts formed by oxaliplatin appear to inhibit DNA replication more effectively than cisplatin adducts, and oxaliplatin has demonstrated activity in tumours with intrinsic or acquired resistance to cisplatin [5–7]. Unlike cisplatin, oxaliplatin has proven activity in colorectal cancer and is a standard backbone of chemotherapy in the palliative and adjuvant settings [8]. Oxaliplatin is generally administered in combination with 5-FU, with which it has demonstrated synergistic activity in preclinical models and in clinical practice [7,9]. Whereas cisplatin is associated with dose-limiting renal toxicity, peripheral neuropathy and cumulative ototoxicity [10], the principal dose-limiting toxicity of oxaliplatin is cumulative sensory peripheral neuropathy, which usually resolves over time. Other oxaliplatin-associated toxicities include neutropenia, diarrhoea and vomiting, which can be managed with appropriate prophylaxis and treatment.

Oxaliplatin has demonstrated in vitro anti-tumour activity in human gastric cancer cell lines [11]. Hence the combined evidence – the efficacy of ECF in gastric cancer, the proven activity of oxaliplatin in combination with 5-FU in colorectal cancer and the favourable toxicity profile of oxaliplatin – provides a strong rationale for investigating oxaliplatin–5-FU combinations in gastric cancer.

2. Establishing the optimal platinum agent in gastric cancer

Using ECF as a reference regimen, the UK National Cancer Research Institute's Phase III REAL-2 study was conducted

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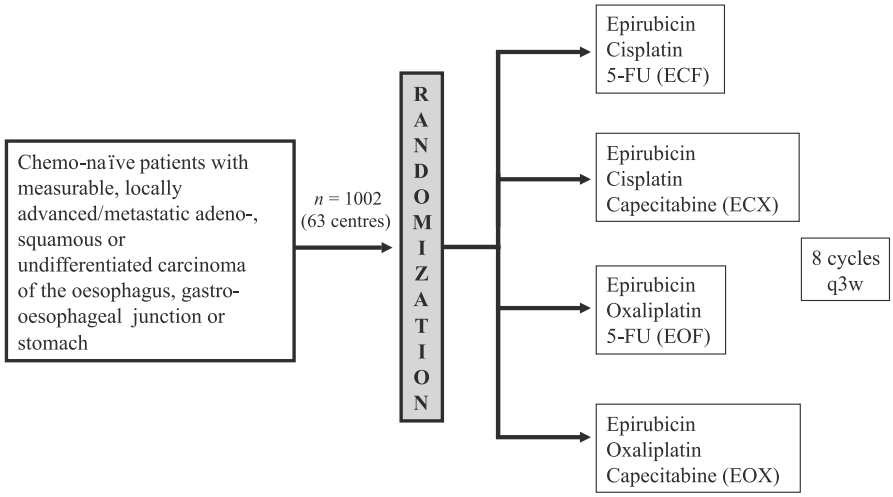

Fig. 1. REAL-2 study design. Doses: Epirubicin 50 mg/m^2; Cisplatin 60 mg/m^2; Oxaliplatin 130 mg/m^2; PVI 5-FU 200 mg/m^2/day; Capecitabine 625 mg/m^2 bid. Primary endpoints: Overall survival for Capecitabine vs. 5-FU and Oxaliplatin vs. Cisplatin (non-inferiority) and between all 4 regimens (superiority). Stratified by: centre; locally advanced vs. metastatic; PS 0/1 vs. 2.

Table 1
REAL-2 study: overall survival results for non-inferiority (2 × 2 comparisons) in the per-protocol population[a]

Treatment arm	Median overall survival (months)	1-year survival (%) [95% CI]	Hazard ratio [95% CI]
5-FU (ECF + EOF)	9.6	39.4 [35.0–44.0]	1
Capecitabine (ECX + EOX)	10.9	44.6 [40.1–49.0]	0.86 [0.8–0.99][b]
Cisplatin (ECF + ECX)	10.0	40.1 [35.7–48.4]	1
Oxaliplatin (EOX + EOF)	10.4	43.9 [39.4–49.0]	0.92 [0.80–1.10][b]

[a] CI, Confidence interval; ECF, Epirubicin–cisplatin–5-fluorouracil; ECX, Epirubicin–cisplatin–capecitabine; EOF, Epirubicin–oxaliplatin–5-FU; EOX, Epirubicin–oxaliplatin–capecitabine.
[b] The upper limit of the 95% CI excludes 1.23, which indicates non-inferiority.

to compare oxaliplatin with cisplatin, and also 5-FU with oral capecitabine, in patients with previously untreated locally advanced or metastatic adeno-, squamous or undifferentiated carcinoma of the oesophagus, gastro-oesophageal junction or stomach. The study used a 2 × 2 factorial study design, in which patients were randomized to one of 4 treatment arms: ECF; ECX (epirubicin–cisplatin–capecitabine); EOF (epirubicin–oxaliplatin–5-FU); or EOX (epirubicin–oxaliplatin–capecitabine) (Fig. 1). In the standard ECF regimen, 5-FU was administered as a protracted venous infusion throughout the period of chemotherapy. In the ECX and EOX regimens, 5-FU was replaced with capecitabine 625 mg/m^2 bid, this dose having been established during a dose-escalation phase of the trial. In the EOF and EOX regimens, cisplatin 60 mg/m^2 intravenously (iv) was replaced by the standard 3-weekly schedule of oxaliplatin 130 mg/m^2 iv. All regimens were administered every 3 weeks for a planned treatment duration of 24 weeks (8 cycles). Computerized tomography (CT) scans were performed at baseline and at 12 and 24 weeks. The primary endpoints of the study were non-inferiority in terms of OS for capecitabine vs. 5-FU and for oxaliplatin versus cisplatin, and superiority in terms of OS between all four treatment regimens.

Final results of the REAL-2 study (1002 patients, median follow-up 17.1 months) were presented at the American Society of Clinical Oncology (ASCO) 2006 annual meeting [12]. Baseline characteristics were well-balanced between the treatment arms. Eighty-nine per cent of patients had Eastern Cooperative Oncology Group performance status 0–1 and 77% had metastatic disease. The non-inferiority primary endpoint was met for both the fluoropyrimidine and platinum comparisons of the respective per-protocol populations (Table 1). Intent-to-treat analysis of data for each of the four treatment regimens showed median OS durations of 9.9 months for ECF, 9.3 months for EOF, 9.9 months for ECX and 11.2 months for EOX. The survival benefit for EOX compared to ECF was statistically significant ($P = 0.020$), with a HR of 0.80 (95% CI, 0.66–0.97). It is notable that the median OS in the EOX arm is one of the longest survival durations reported in a large multicentre study in advanced gastric cancer. The overall response rates (ORR) (complete response + partial response) were consistently high at 40.7%, 46.4%, 42.4% and 47.9% for the ECF, ECX, EOF and EOX regimens, respectively, with no significant difference between the groups. Grade 3/4 neutropenia was more

commonly associated with cisplatin (ECF, 41.7%; ECX, 51.1%) than with oxaliplatin (EOF, 29.9%; EOX, 27.6%). Grade 3–4 non-haematological toxicity was reported for 36%, 33%, 42% and 45% of patients in the ECF, ECX, EOF and EOX groups, respectively.

We can conclude that oxaliplatin may be substituted for cisplatin in ECF, without decreasing the efficacy of treatment. 5-FU may also be replaced with capecitabine, and, since capecitabine is administered orally, the delivery of chemotherapy will be simplified. Finally, EOX seems to be associated with significantly improved efficacy compared to ECF.

3. Phase II studies of oxaliplatin in gastric cancer

The activity of oxaliplatin-based chemotherapy in gastric cancer is further supported by the results of several Phase II studies. When administered as first-line chemotherapy for advanced or metastatic gastric cancer, FOLFOX (5-FU–leucovorin–oxaliplatin) regimens have demonstrated ORRs of 38% to 55%, median times to progression (TTPs) of 4.9 months to 7.7 months and median OS durations of 8.0 months to 11.4 months [13–22]. Weekly 5-FU–leucovorin–oxaliplatin (FUFOX) demonstrated a favourable toxicity profile and achieved an ORR of 54%, median TTP of 6.5 months and a median OS duration of 11.4 months in a Phase II study in 48 patients with previously untreated metastatic gastric cancer [23].

4. Alternative cytotoxic combinations in advanced gastric cancer

The results of the TAX 325 study have established the role of docetaxel (Taxotere®) in advanced gastric cancer and introduced a new standard – docetaxel–cisplatin–5-FU (TCF) – in this setting [24–26] (see Ajani, this issue). In this large Phase III study of 445 patients with advanced gastric or gastro-oesophageal junction adenocarcinoma who had received no prior palliative treatment, TCF achieved a median TTP of 5.6 months, a median OS duration of 9.2 months and an ORR of 37%. All of these parameters were significantly improved compared with the reference regimen CF. A novel cytotoxic combination of docetaxel plus oxaliplatin has been investigated in several small Phase II studies with promising results [27,28] (see van Cutsem, this issue). Taking aspects from all of these studies – the REAL-2 study, the TAX 325 study and the preliminary oxaliplatin–docetaxel doublet studies – a large Phase II study (GATE study) will soon investigate three cytotoxic combinations: docetaxel–oxaliplatin; docetaxel–oxaliplatin–leucovorin–5-FU; and docetaxel–oxaliplatin–capecitabine in 270 patients with previously untreated advanced gastric or gastro-oesophageal junction adenocarcinoma.

5. Conclusions

A number of active agents are now available for the treatment of advanced gastric cancer. The newer agents, such as oxaliplatin, capecitabine and docetaxel, offer the potential to build on established strategies, in particular platinum–fluoropyrimidine combinations, and to improve both the efficacy and tolerability of chemotherapy. Using ECF as a reference regimen, the REAL-2 study showed that oxaliplatin may be substituted for cisplatin and that capecitabine may be substituted for 5-FU with no adverse effect on efficacy, improved convenience and favourable safety. These encouraging results support the potential of oxaliplatin–fluoropyrimidine-containing chemotherapy in gastric cancer and provide a new core on which to add other agents, such as docetaxel and the biologics, in future investigations.

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