ORIGINAL ARTICLE

Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

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ABSTRACT

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outh (F.D.) — all in the United Kingdom.

BACKGROUND

We evaluated capecitabine (an oral fluoropyrimidine) and oxaliplatin (a platinum com-
pound) as alternatives to infused fluorouracil and cisplatin, respectively, for untreated
advanced esophagogastric cancer.

METHODS

In a two-by-two design, we randomly assigned 1002 patients to receive triplet ther-
apy 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). The primary end point was noninferiority in overall survival for
the triplet therapies containing capecitabine as compared with fluorouracil and for
those containing oxaliplatin as compared with cisplatin.

RESULTS

For the capecitabine–fluorouracil comparison, the hazard ratio for death in the
capecitabine group was 0.86 (95% confidence interval [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 noninferiority 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; 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 signifi-
cantly among the regimens. Toxic effects of capecitabine and fluorouracil were simi-
lar. As compared with cisplatin, oxaliplatin was associated with lower incidences of
grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with
slightly higher incidences of grade 3 or 4 diarrhea and neuropathy.

CONCLUSIONS

Capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively,
in patients with previously untreated esophagogastric cancer. (Current Controlled
Trials number, ISRCTN51678883.)

GASTRIC AND ESOPHAGEAL CANCERS are the second and sixth most common causes of cancer-related deaths worldwide, respectively.[1] Most patients present with advanced, inoperable, or metastatic disease, and 5-year survival rates are approximately 10 to 15%. Palliative chemotherapy for advanced disease improves survival, as compared with the best supportive care.[2-4] There is no single, global standard regimen for the first-line treatment of advanced disease. Of the available regimens, the regimen containing epirubicin, cisplatin, and infused fluorouracil (ECF) is widely used in Europe, particularly in the United Kingdom, on the basis of the results of two randomized studies[5,6] and a recent meta-analysis.[7] ECF is also routinely used in the perioperative treatment of esophagogastric cancer.[8]

The fluorouracil in the ECF regimen is continuously infused through a central venous access device (CVAD) and an ambulatory infusion pump. This delivery system is inconvenient and can be associated with infection and thrombosis. Patients with cancer generally prefer oral alternatives to intravenous chemotherapy, provided that efficacy is maintained.[9-11] Capecitabine is an oral fluoropyrimidine that is activated in tumor tissue by a three-step enzymatic conversion culminating with thymidine phosphorylase.[12] Capecitabine is an established oral alternative to fluorouracil for the treatment of early and advanced colorectal cancer,[13,14] and it has been safely combined with oxaliplatin (an intravenously administered platinum complex) for treating advanced colorectal cancer without a loss of efficacy.[15-17] Phase 1 evaluation in esophagogastric cancer supports the safety of capecitabine when administered twice daily[18] and in combination with epirubicin and cisplatin,[19] with indications of efficacy.[19,20]

Cisplatin in the ECF regimen causes renal toxicity, high-frequency sensorineural hearing loss, emesis, and peripheral neuropathy. The required intravenous hydration lengthens outpatient visits or necessitates overnight admission. By contrast, oxaliplatin can be given as an intravenous infusion during a 2-hour period.

Our phase 3 trial, called Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2), was designed to determine whether fluorouracil can be replaced by capecitabine and cisplatin by oxaliplatin in the regimen of ECF. An interim analysis that we performed after the recruitment of 204 patients (which was reported previously)[21] showed the safety of escalating the dose of capecitabine from 1000 mg per square meter of body-surface area to 1250 mg per square meter daily. The primary goal of the study was to investigate whether capecitabine and oxaliplatin are at least as effective as fluorouracil and cisplatin, respectively, in terms of overall survival. Other planned analyses included assessments of overall survival among the regimens, progression-free survival, response rates, safety, and quality of life. Investigators who participated in the REAL-2 study are listed in the Appendix.

METHODS

PATIENTS

Patients who were 18 years of age or older were eligible if they had a histologically proven adenocarcinoma, squamous-cell carcinoma, or undifferentiated carcinoma of the esophagus, gastroesophageal junction, or stomach that was locally advanced (inoperable) or metastatic. Other inclusion criteria were measurable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST)[22]; an Eastern Cooperative Oncology Group performance status of 0 to 2 (ranging from normal to symptomatic but in bed less than half the day); and adequate renal, hepatic, and hematologic function. Patients without measurable disease and with a positive resection margin after radical surgery (tumor within 1 mm of the resection margin) were also eligible owing to their poor prognosis; these patients were evaluated for survival only.

Major exclusion criteria were previous chemotherapy or radiotherapy (unless the latter was adjuvant treatment with relapse outside the radiotherapy field), uncontrolled cardiac disease, or other clinically significant, uncontrolled coexisting illness or previous or concurrent cancer. The study was approved by a multicenter research ethics committee and the scientific review and ethics committee at each of the participating institutions. All patients provided written informed consent, and the study was carried out in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.

TRIAL DESIGN

The trial was overseen by an independent data and safety monitoring committee that met after three planned interim analyses. Committee members

met when 80 patients had been recruited, to confirm the decision to escalate the capecitabine dose from 1000 mg per square meter to 1250 mg per square meter daily; when 204 patients had been recruited, to confirm the safety of the escalation in the capecitabine dose[21]; and when 724 patients had been recruited. There were no formal stopping rules or formal review of the primary end point, and the committee recommended continuation of the trial after each review.

The data were collected and analyzed by the Gastrointestinal Unit Trials Office Research Team at the Royal Marsden Hospital. The trial was sponsored by the Royal Marsden Hospital and adopted by the Upper Gastrointestinal Clinical Studies Group of the United Kingdom's National Cancer Research Institute. Hoffmann–La Roche provided the investigators with capecitabine at a cost equivalent to that of fluorouracil, and Sanofi-Aventis provided oxaliplatin at no cost. The pharmaceutical companies were not involved in the design of the study, in the analysis of data, or in the preparation of the manuscript, although representatives of the companies reviewed the first draft of the manuscript.

TREATMENT

With a two-by-two design and the use of random permuted blocks, we randomly assigned patients to one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). Study-group assignments were made by means of a telephone call to an independent randomization service at the Clinical Trials and Statistics Unit of the Institute of Cancer Research, United Kingdom. Patients were stratified according to performance status, treatment center, and extent of disease (locally advanced or metastatic). Both investigators and patients were aware of study-group assignments.

On day 1 of every 3-week cycle, patients in all study groups received an intravenous bolus of epirubicin (at a dose of 50 mg per square meter); cisplatin (at a dose of 60 mg per square meter) was given intravenously with hydration in the ECF and ECX groups, and oxaliplatin (at a dose of 130 mg per square meter) was administered intravenously during a 2-hour period in the EOF and EOX groups. Fluorouracil (at a daily dose of 200 mg per square meter) and capecitabine (at a twice-

daily dose of 625 mg per square meter) were given throughout treatment in the appropriate groups. Fluorouracil was administered through a CVAD with an empirical dose of 1 mg of warfarin daily for thromboprophylaxis. Antiemetic prophylaxis was routinely administered as described previously.[21] Treatment cycles were repeated every 3 weeks for a maximum of eight cycles unless there was evidence of disease progression or unacceptable toxicity, or the patient withdrew consent or died.

Investigators graded all adverse events and toxic effects according to the National Cancer Institute's Common Toxicity Criteria, version 2.0. Adverse events during the previous cycle of treatment and measures of hematologic and biochemical function were recorded at each treatment visit. Dose modifications for each regimen were predefined for hematologic and nonhematologic toxic effects, as reported previously.[21]

EVALUATION AND OUTCOMES

Pretreatment evaluation included a full medical history, physical examination, a complete blood count, clotting analysis, serum biochemical analysis, 24-hour urinary clearance or EDTA testing, and electrocardiography (with or without echocardiography or multiple-gated acquisition scanning); audiography was performed when indicated. Baseline chest radiography and computed tomography of the chest, abdomen, and pelvis (with or without upper gastrointestinal endoscopy) were performed within 28 days before the start of therapy.

Tumor measurements were performed at baseline and at 12 and 24 weeks, and the response to treatment was recorded according to RECIST guidelines.[22] The quality of life was assessed with the use of the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, version 3,[23] before randomization and at 3, 6, 9, and 12 months.

STATISTICAL ANALYSIS

The primary objective was to determine noninferiority in overall survival for the triplet combinations containing capecitabine as compared with those containing fluorouracil (ECX or EOX vs. ECF or EOF) and for the combinations containing oxaliplatin as compared with those containing cisplatin (EOF or EOX vs. ECF or ECX) in the two-by-two comparisons. On the basis of a 1-year survival rate of 35% for patients receiving ECF,

Figure 1. Enrollment and Outcomes.

CVAD denotes central venous access device.
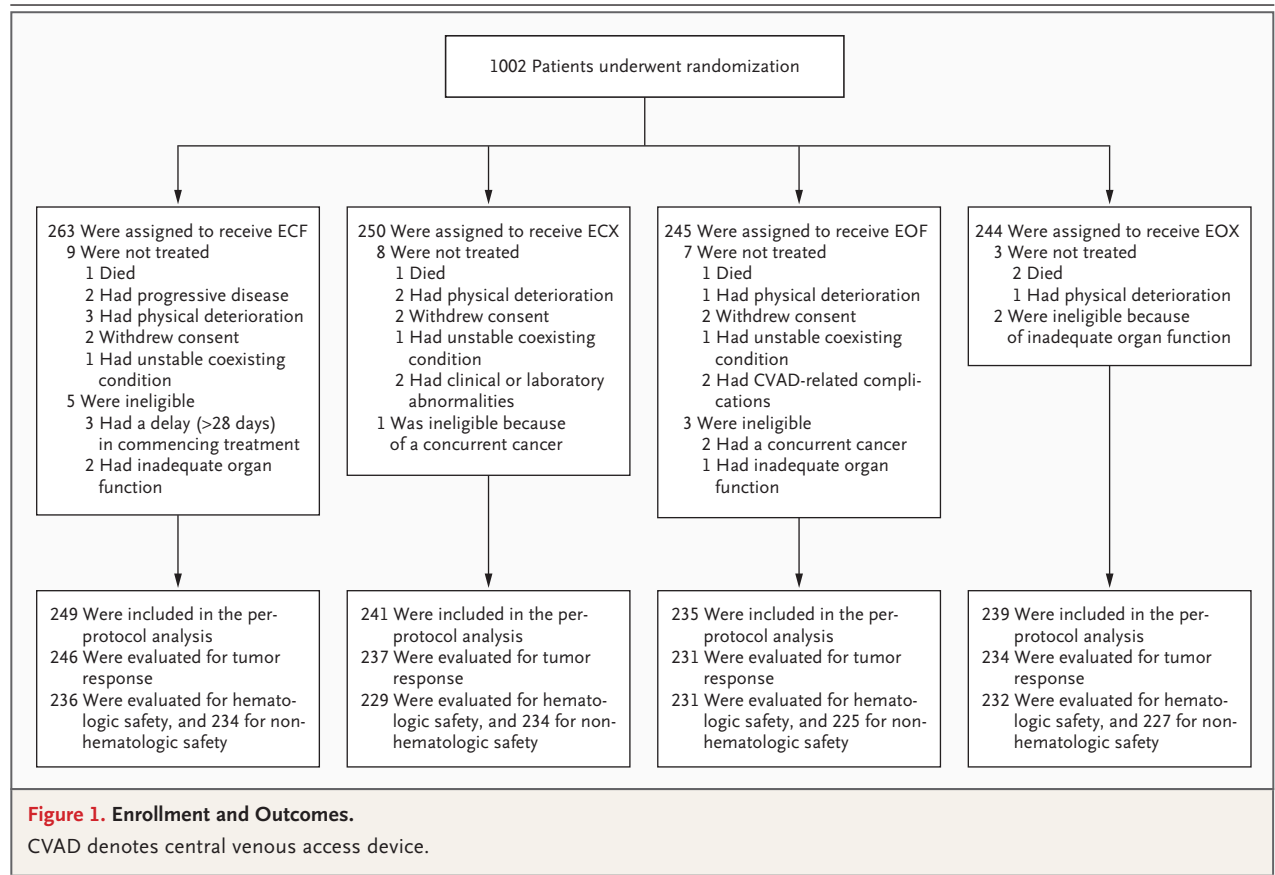
1000 patients were needed (250 per group) to show noninferiority at a 1-year survival rate of 27.5 to 35.0% with a power of 80% and a one-sided alpha of 0.05 for each of the two comparisons. The upper limit of the 95% confidence interval for the unadjusted hazard ratio for death from the Cox regression model for the experimental regimen, as compared with the standard regimen, was required to be less than 1.23 to show noninferiority. The noninferiority analysis was performed in the per-protocol population (i.e., patients receiving at least one cycle of chemotherapy).

A secondary objective was to assess overall survival in the intention-to-treat population for the two-by-two comparisons and among the four treatment groups. Secondary end points included progression-free survival, response rates (according to RECIST criteria), toxic effects, and quality of life.

Overall survival was calculated from the date of randomization to the date of death from any cause. Progression-free survival was calculated from the date of randomization to the first date of documented progressive disease or the date of death from any cause. Data from patients who were alive and from those who were free of progression were censored at the date of the last follow-up visit for overall and progression-free survival, respectively. Survival was calculated with the use of the Kaplan–Meier method, and hazard ratios were calculated with the use of the Cox proportional-hazards model. For the secondary analyses, we compared rates of survival in the intention-to-treat population with the use of the unadjusted log-rank test; for the planned comparisons among study groups, the comparator was the ECF group. The planned Cox-regression multivariate analysis of survival included age, sex, performance status, extent of disease, tumor location, and histologic analysis. Overall response and rates of toxic effects were compared with the use of a chi-square test. All the reported P values are two-sided and have not been adjusted for multiple testing; P values of less than 0.05 were considered to indicate statistical significance.

Table 1. Baseline Demographic and Clinical Characteristics (Per-Protocol Population).*

Variable	ECF (N = 249)	ECX (N = 241)	EOF (N = 235)	EOX (N = 239)
Age (yr)				
Median	65	64	61	62
Range	22–83	25–82	33–78	25–80
Sex (%)				
Male	81.1	80.5	81.3	82.8
Female	18.9	19.5	18.7	17.2
Subsite of tumor (%)				
Esophagus	34.9	29.5	39.6	34.3
Gastroesophageal junction	28.9	28.2	23.4	22.2
Stomach	36.1	42.3	37.0	43.5
Performance-status score (%)†				
0 or 1	88.4	87.6	91.5	90
2	11.6	12.4	8.5	10.0
Extent of disease (%)				
Metastatic	79.5	76.8	77.0	75.7
Locally advanced	20.5	23.2	23.0	24.3
Type of tumor (%)				
Adenocarcinoma	90.0	89.6	86.0	87.4
Squamous-cell carcinoma	7.6	9.5	12.8	12.1
Undifferentiated carcinoma	2.4	0.8	1.3	0.4
No. of metastatic sites (%)				
0 or 1	63.5	59.3	60.9	64.4
≥2	36.5	40.7	39.1	35.6
Previous surgery (%)	7.6	7.5	7.7	8.8

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).
† Performance was evaluated according to guidelines of the Eastern Cooperative Oncology Group, with a score of 0 indicating normal performance status, 1 mildly symptomatic, 2 symptomatic but in bed less than half the day, 3 symptomatic and in bed more than half the day, and 4 in bed the whole day.

RESULTS

PATIENTS

Between June 2000 and May 2005, a total of 1002 patients in the intention-to-treat population underwent randomization — 263 to the ECF group, 250 to the ECX group, 245 to the EOF group, and 244 to the EOX group — at 59 centers in the United Kingdom and 2 in Australia. Since 38 patients were ineligible or withdrew before treatment, the per-protocol population consisted of 964 patients (Fig. 1). The study groups were well balanced in terms of their baseline characteristics (Table 1). Most patients had metastatic adenocarcinoma, and there was a relatively even distribution of patients among the three tumor subsites. Patients whose tumors had positive margins after resection constituted less than 1.6% of the per-protocol population.

CHEMOTHERAPY

The median number of cycles administered was six in each study group. The median actual dose intensities of the epirubicin, platinum, and fluoropyrimidine drugs were similar in all groups. (For details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org.) The mean number of days of a delay in treat-

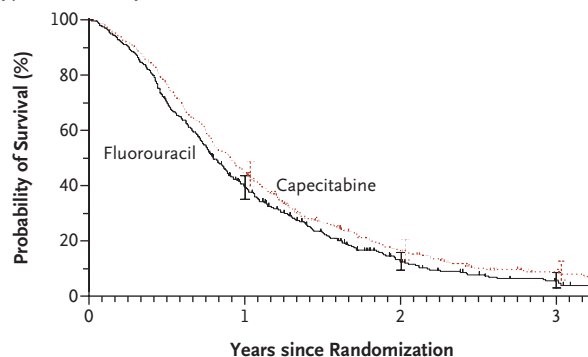**Figure 2. Kaplan–Meier Estimates of Overall Survival.**

Panel A shows overall survival according to a two-by-two comparison in the per-protocol population between the capecitabine and fluorouracil regimens; the hazard ratio for death in the capecitabine groups was 0.86 (95% CI, 0.80 to 0.99). The upper limit of the 95% confidence interval for the hazard ratio was well below the noninferiority margin of 1.23. The median survival and 1-year survival rate for capecitabine as compared with fluorouracil were 10.9 months versus 9.6 months and 44.6% (95% CI, 40.1 to 49.0) versus 39.4% (95% CI, 35.0 to 44.0). Panel B shows overall survival according to a two-by-two comparison in the per-protocol population between the oxaliplatin and cisplatin regimens; the hazard ratio for death in the oxaliplatin groups was 0.92 (95% CI, 0.80 to 1.10). The upper limit of the 95% confidence interval was well below the noninferiority margin. The median survival and 1-year survival rate for oxaliplatin as compared with cisplatin were 10.4 months versus 10.0 months and 43.9% (95% CI, 39.4 to 48.4) versus 40.1% (95% CI, 35.7 to 44.4). Panel C shows overall survival in the intention-to-treat population between the group that received epirubicin and oxaliplatin plus capecitabine (EOX) and the group that received epirubicin and cisplatin plus fluorouracil (ECF). The hazard ratio for death in the EOX group, as compared with the ECF group, was 0.80 (95% CI, 0.66 to 0.97; P=0.02).

A Fluoropyrimidine Comparison

No. at Risk				
Fluorouracil	484	178	37	8
Capecitabine	480	206	52	12

B Platinum Comparison
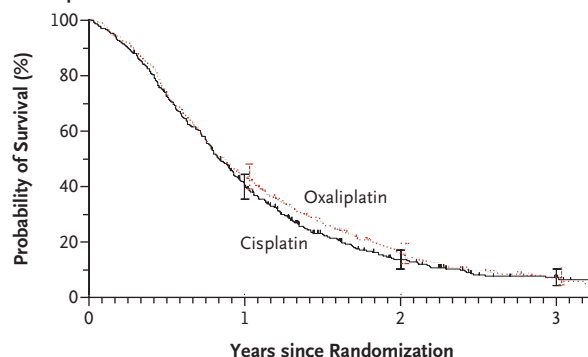
No. at Risk				
Cisplatin	490	187	41	10
Oxaliplatin	474	198	48	10

C Comparison between ECF and EOX

No. at Risk				
ECF	263	91	20	5
EOX	244	109	30	7

ment per patient was marginally lower in the EOF group than in the ECF group (5.8 vs. 7.7 days, P=0.01). The percentages of patients undergoing at least one dose reduction of one of the drugs in the regimen were similar in all the study groups (ECF, 35%; ECX, 40%; EOF, 39%; and EOX, 42%).

STUDY END POINTS

Overall Survival

The database was locked on March 1, 2006. At a median follow-up of 17.1 months, 850 events had occurred. The median follow-up was 17.5 months in the ECF group, 17.6 months in the ECX group, 19.3 months in the EOF group, and 18.9 months in the EOX group. For the survival analysis, the test for interaction among the treatment variables in the pooled two-by-two comparisons did not reveal any interaction between the fluoropyrimidine and platinum groups (P=0.36).
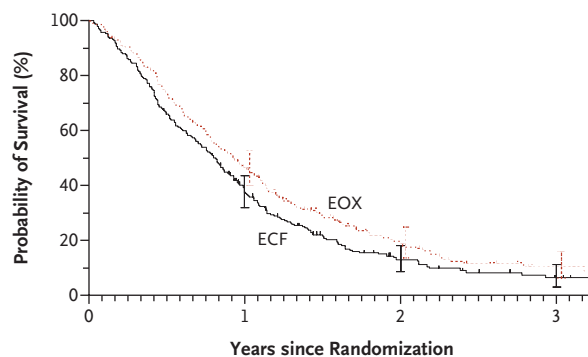
For the primary end point, the unadjusted hazard ratio for death for the noninferiority comparison of capecitabine with fluorouracil was 0.86 (95% confidence interval [CI], 0.80 to 0.99); for the comparison of oxaliplatin with cisplatin, the hazard ratio was 0.92 (95% CI, 0.80 to 1.10) (Fig. 2A and 2B). The upper limits of the 95% confidence intervals for both hazard ratios (0.99 and 1.10, respectively) were well below the prespecified margin of 1.23, thereby showing noninferiority of both capecitabine and oxaliplatin in the two-by-two comparison.

Table 2. Analysis of Efficacy (Intention-to-Treat Population).*

Variable	ECF (N = 263)	ECX (N = 250)	EOF (N = 245)	EOX (N = 244)
Death				
No. of patients	225	213	213	199
Hazard ratio (95% CI)		0.92 (0.76–1.11)	0.96 (0.79–1.15)	0.80 (0.66–0.97)
P value		0.39	0.61	0.02
Overall survival				
Median — mo	9.9	9.9	9.3	11.2
At 1 yr — % (95% CI)	37.7 (31.8–43.6)	40.8 (34.7–46.9)	40.4 (34.2–46.5)	46.8 (40.4–52.9)
Progression-free survival				
Median — mo	6.2	6.7	6.5	7.0
Patients who had progression or died	237	231	221	213
Hazard ratio (95% CI)		0.98 (0.82–1.17)	0.97 (0.81–1.17)	0.85 (0.70–1.02)
P value		0.80	0.77	0.07
Response				
Overall — % (95% CI)†	40.7 (34.5–46.8)	46.4 (40.0–52.8)	42.4 (36.1–48.8)	47.9 (41.5–54.3)
Complete — %	4.1	4.2	2.6	3.9
Partial — %	36.6	42.2	39.8	44.0
P value		0.20	0.69	0.11

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).
† Overall response could be evaluated in 246 patients in the ECF group, 237 patients in the ECX group, 231 patients in the EOF group, and 234 patients in the EOX group.

Noninferiority for both comparisons was maintained in the multivariate analysis; factors that were included in the model were performance status, extent of disease, and age; factors that were excluded were primary tumor site, sex, and results of histologic analysis. The adjusted hazard ratio for death in the capecitabine groups, as compared with the fluorouracil groups, was 0.89 (95% CI, 0.77 to 1.02); for the oxaliplatin groups, as compared with the cisplatin groups, it was 0.95 (95% CI, 0.82 to 1.09). All tests for heterogeneity with regard to treatment effect, overall survival, and prognostic factors, including the primary site and the results of histologic analysis, for the two-by-two comparisons did not reveal any significant heterogeneity (P>0.05 in all cases).

In the intention-to-treat analysis, overall survival in the capecitabine groups did not differ significantly from that in the fluorouracil groups (hazard ratio for death, 0.88; 95% CI, 0.77 to 1.00; P=0.06), nor did overall survival in the oxalipla-

tin groups differ significantly from that in the cisplatin groups (hazard ratio, 0.91; 95% CI, 0.79 to 1.04; P=0.16). Table 2 shows the results of the prespecified analysis and 95% confidence intervals for overall survival in each of the study groups.

The 1-year survival rate in the ECF group was 37.7%, and the median survival was 9.9 months. Survival was longer in the EOX group than in the ECF group, with a 1-year survival rate of 46.8% and a median survival of 11.2 months (hazard ratio, 0.80; 95% CI, 0.66 to 0.97; P=0.02) (Fig. 2C). Of 964 patients, 135 (14.0%) received second-line therapy; of these patients, the numbers were balanced among the groups.

Progression-free Survival and Response
Progression-free survival did not differ significantly in the two-by-two comparisons in the intention-to-treat population (Fig. 3A and 3B) or in the comparisons between each study group and the ECF group (Table 2). The overall response rate,

which was 40.7% (95% CI, 34.5 to 46.8) in the ECF group, did not differ significantly among the groups (Table 2).

SAFETY AND QUALITY OF LIFE

Table 3 presents the incidence of major adverse events according to the study group. As compared with cisplatin, oxaliplatin was associated with significantly less grade 3 or 4 neutropenia and alopecia but significantly more grade 3 or 4 diarrhea and peripheral neuropathy. Grade 3 or 4 neutropenia and the hand–foot syndrome were more frequent in the ECX group than in the ECF group. There was a small increase in stomatitis in the EOF group and increased lethargy in the EOX group, as compared with the ECF group. Grade 1 or 2 elevations in creatinine occurred in each group: in 19.2% of patients in the ECF group, 16.5% in the ECX group, 12.4% in the EOF group, and 7.9% in the EOX group. There was a trend toward less elevated creatinine levels during treatment in the oxaliplatin groups, as compared with the cisplatin groups (P=0.003 by the chi-square test for trend). The overall rate of thromboembolic events was 11.4% (95% CI, 9.4 to 13.4), and the rate was significantly lower in the oxaliplatin groups than in the cisplatin groups (7.6% vs. 15.1%, P<0.001) but did not differ significantly between the groups receiving capecitabine and those receiving fluorouracil (10.4% vs. 12.4%, P=0.33). At 60 days, rates of death from any cause did not differ significantly among the four study groups (Table 3).

At baseline and 12 weeks, rates of compliance in responding to the quality-of-life questionnaire were 96% and 70%, respectively. Mean scores on the questionnaire's Global Health Status subscale at baseline and at 12 weeks showed no significant differences between the ECF group and the other groups (data not shown).

DISCUSSION

This randomized, phase 3 study of triplet cytotoxic therapy for advanced esophagogastric cancer showed that oral capecitabine is at least as effective as infused fluorouracil and that oxaliplatin (which does not require hydration) is at least as effective as cisplatin (which does require hydration) with respect to overall survival. A planned multivariate analysis confirmed the robustness
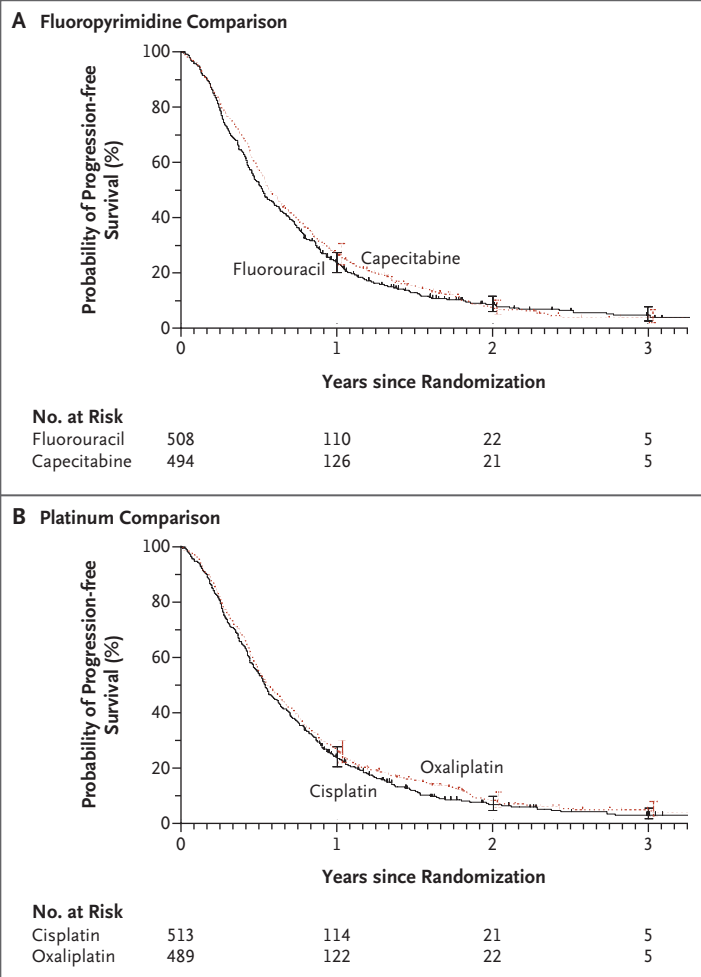
Figure 3. Kaplan–Meier Estimates of Progression-free Survival.

Panel A shows a comparison of progression-free survival in the intention-to-treat population between the capecitabine and fluorouracil regimens. The hazard ratio for progression with the capecitabine regimens was 0.92 (95% CI, 0.81 to 1.05; P=0.22). Panel B shows progression-free survival in the intention-to-treat population between the oxaliplatin and cisplatin regimens. The hazard ratio for progression with the oxaliplatin regimens was 0.92 (95% CI, 0.80 to 1.04; P=0.19).

of the noninferiority result for the primary analysis. Performance status, extent of disease, and age were included in the model. The subsite of the tumor (esophagus, gastroesophageal junction, or stomach) and the results of histologic analysis (adenocarcinoma or squamous-cell carcinoma) did not significantly affect survival; these variables were excluded from the model. There was a nonsignificant trend toward improved survival in the capecitabine groups as compared with the fluoro-

Table 3. Most Common Treatment-Related Adverse Events (Safety Population).*

Adverse Event	ECF (N=234)		ECX (N=234)		EOF (N=225)		EOX (N=227)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
				percent				
Anemia†	78.4	13.1	79.5	10.5	65.8	6.5‡	64.2	8.6
Thrombocytopenia†	14.5	4.7	17.0	4.8	13.4	4.3	21.1	5.2
Neutropenia†	73.6	41.7	85.6	51.1‡	68.4	29.9§	62.9	27.6§
Febrile neutropenia†	13.2	9.3	10.5	6.7	11.5	8.5	9.8	7.8
Diarrhea	39.3	2.6	41.9	5.1	62.7	10.7§	61.7	11.9§
Stomatitis	50.9	1.3	39.3	1.7	44.4	4.4‡	38.1	2.2
Hand–foot syndrome	29.8	4.3	45.9	10.3‡	28.9	2.7	39.3	3.1
Nausea and vomiting	79.1	10.2	82.1	7.7	83.1	13.8	78.9	11.4
Peripheral neuropathy	30.0	0.4	36.3	1.7	79.6	8.4§	83.7	4.4§
Lethargy	89.7	16.6	92.7	15.5	90.2	12.9	96.1	24.9‡
Alopecia¶	81.5	44.2	82.5	47.4	75.4	27.7§	74.2	28.8§
Thromboembolism‖	16.9	NA	13.3	NA	7.7§	NA	7.5§	NA
Death within 60 days (95% CI)**	7.2 (4.7–11.1)		5.6 (3.4–9.3)		5.7 (3.4–9.5)		6.1 (3.8–10.0)	

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). NA denotes not applicable.
† This side effect of treatment was measured in the hematologic-safety population, consisting of 236 patients in the ECF group, 229 patients in the ECX group, 231 patients in the EOF group, and 232 patients in the EOX group.
‡ P<0.01 to P<0.05 for the comparison with the ECF group.
§ P<0.001 to P<0.01 for the comparison with the ECF group.
¶ The highest grade of alopecia was grade 2, which is listed in the grade 3 or 4 column.
‖ The diagnosis of thromboembolism was made only in the per-protocol population.
** Death within 60 days after randomization was evaluated only in the intention-to-treat population.

uracil groups in the intention-to-treat analysis. Progression-free survival was similar in the fluoropyrimidine groups and the platinum groups.

The 1-year survival rate (37.7%), median survival (9.9 months), and overall rate of response (40.7%) in the ECF group were consistent with those reported in studies previously.[5,6] In the planned analysis of survival among the groups, overall survival was improved in the EOX group (11.2 months), as compared with the ECF group (hazard ratio for death, 0.80; 95% CI, 0.66 to 0.97; P=0.02). Response rates were highest in the EOX group (47.9%), followed by the ECX group (46.4%), but did not differ significantly from those in the ECF group. Progression-free survival in the EOX group (7.0 months) did not differ significantly from that in the ECF group (6.2 months) (hazard ratio, 0.85; 95% CI, 0.70 to 1.02; P=0.07). However, there was concordance between the hazard ratios

and confidence intervals for overall and progression-free survival for all study groups, including the EOX group, which suggests that there was a similar magnitude of benefit with respect to both these efficacy end points.

Our results for the fluoropyrimidine comparison are supported by the results of a recent randomized trial involving patients with gastric cancer, which showed that capecitabine was not inferior to fluorouracil when substituted in the cisplatin–fluorouracil regimen.[24] The interim results of a recent randomized trial assessing the substitution of oxaliplatin for cisplatin in a regimen combining infusion of fluorouracil over a period of 2 days with platinum indicated a nonsignificant trend toward a longer time to progression in the oxaliplatin group, as compared with the cisplatin group.[25]

There were no significant differences in dose

intensity among the regimens tested. Fluoropyrimidine-related adverse events were similar in the capecitabine groups and the fluorouracil groups. However, there was an increase in grade 3 or 4 neutropenia (but not febrile neutropenia) and an expected modest increase in the incidence of grade 3 or 4 hand–foot syndrome in the ECX group, as compared with the ECF group. With the education and monitoring of patients, the severity of capecitabine-related hand–foot syndrome can be reduced. CVAD-related complications requiring removal of the device occurred in 10% of patients treated with fluorouracil. There were significantly lower incidences of grade 3 or 4 neutropenia, thromboembolism, grade 2 alopecia, and elevation of serum creatinine levels in the oxaliplatin groups than in the ECF group. However, there were modest increases in the incidences of grade 3 or 4 peripheral neuropathy and diarrhea in the oxaliplatin groups. Surprisingly, the incidence of emesis was not decreased in the oxaliplatin group, which may reflect improvements in antiemetic therapy. The quality of life did not differ among the groups.

There is currently no universal standard regimen for the treatment of esophagogastric cancer. The cisplatin–fluorouracil regimen is commonly used in the treatment of gastric cancer, with disappointing results; the 1-year survival rate is approximately 30%, the median survival is 8 months, and response rates are 20 to 30%.[26,27] In randomized studies, the substitution of irinotecan for cisplatin did not improve efficacy,[26] but the addition of docetaxel to cisplatin–fluorouracil resulted in modest increases in the time to progression, overall survival, and quality of life, albeit at the expense of increased toxicity.[27] However, further progress is required, and the next generation of clinical trials involving patients with esophagogastric cancer will incorporate targeted agents into optimized cytotoxic platforms, such as EOX (on the basis of efficacy, ease of administration, and toxic effects), in tandem with correlative translational research in order to improve outcomes further.

APPENDIX

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