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TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG

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ABSTRACT

Background. Postoperative chemoradiation and perioperative chemotherapy using epirubicin/cisplatin/5-fluorouracil (ECF) represent two standards of care for resectable gastric cancer. In the TOPGEAR (Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma) trial, we hypothesized that adding preoperative chemoradiation to perioperative ECF will improve survival; however, the safety and feasibility of preoperative chemoradiation have yet to be determined.

Methods. TOPGEAR is an international phase III trial in which patients with adenocarcinoma of the stomach were randomized to perioperative ECF alone or with preoperative chemoradiation. The ECF-alone group received three preoperative cycles of ECF, while the chemoradiation group received two cycles of preoperative ECF followed by chemoradiation. Both groups received three postoperative cycles of ECF. A planned interim analysis of the first 120 patients was conducted, and was reviewed by the Independent Data Safety Monitoring Committee to assess treatment compliance, toxicity/safety, and response rates.

Results. The proportion of patients who received all cycles of preoperative chemotherapy was 93% (ECF group) and 98% (chemoradiation group), while 65 and 53%, respectively, received all cycles of postoperative chemotherapy. Overall, 92% of patients allocated to preoperative chemoradiation received this treatment. The proportion of patients proceeding to surgery was 90% (ECF group) and 85% (chemoradiation group). Grade 3 or higher surgical complications occurred in 22% of patients in both groups. Furthermore, grade 3 or higher gastrointestinal toxicity occurred in 32% (ECF group) and 30% (chemoradiation group) of patients, while hematologic toxicity occurred in 50 and 52% of patients.

Conclusions. These results demonstrate that preoperative chemoradiation can be safely delivered to the vast majority of patients without a significant increase in treatment toxicity or surgical morbidity.

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The US Intergroup 0116 and UK Medical Research Council MAGIC trials have established postoperative chemoradiation and perioperative chemotherapy with epirubicin, cisplatin, and 5-fluorouracil (ECF) as standards of care for adjuvant therapy of resectable gastric cancer in Western countries.[1,2] By analysing failure patterns in the INT0116 and MAGIC trials, each approach appears to improve survival through different mechanisms. The perioperative ECF approach reduces systemic failure, while postoperative chemoradiation improves locoregional control. Since both strategies provide moderate gains in survival, we hypothesized that adding chemoradiation to standard perioperative ECF chemotherapy will achieve even greater survival gains in a similar patient population. Furthermore, we believe there are advantages to testing the addition of chemoradiation by administering it in the preoperative rather than postoperative setting. Advantages of preoperative therapy include the potential for tumor downstaging with an increase in the complete R0 resection rate, and better patient tolerability. However, the safety and feasibility of preoperative chemoradiation for gastric cancer have yet to be determined and are areas of concern for clinicians. The strategy of preoperative chemoradiation for gastric cancer has thus far only been tested in a small number of phase II studies.[3,4] In addition, preoperative chemoradiation has now become the standard of care for patients with oesophageal and gastroesophageal junction tumors, thereby lending further support to its use in gastric cancer.[5]

TOPGEAR (Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma) is a randomized, phase III trial that compares control arm therapy of perioperative ECF chemotherapy (as per the MAGIC trial) with experimental arm therapy of perioperative ECF plus preoperative chemoradiation.[6] This trial is an international, intergroup collaboration led by the Australasian Gastro-Intestinal Trials Group (AGITG) and the National Health and Medical Research Council Clinical Trials Centre, in collaboration with the Trans-Tasman Radiation Oncology Group (TROG), European Organisation for Research and Treatment of Cancer (EORTC), and the Canadian Cancer Trials Group (CCTG). TOPGEAR is a currently accruing trial with a target sample size of 752 patients. In this article, we report the results of a planned interim analysis of the first 120 patients to assess safety/toxicity, feasibility, and preliminary efficacy of preoperative chemoradiation.

METHODS

Study Design

The study design is summarized as a detailed description of the full trial protocol has been reported.[6]

The primary objective of the trial is to investigate whether perioperative ECF plus preoperative chemoradiation improves overall survival compared with perioperative ECF alone. As preoperative chemoradiation is untested in the setting of gastric cancer, the trial protocol included a pre-planned interim analysis after accrual of 120 patients, with the aim of assessing safety/toxicity, feasibility, and preliminary efficacy of preoperative chemoradiation.

Participants

Eligible patients were those with histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert types II and III) that was stage IB (T1N1 only) to IIIC (i.e. T3–T4 and/or N-positive) and that was considered operable following initial staging investigations. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and adequate bone marrow, liver, and renal function. The protocol was approved by the Clinical Research Ethics Committee of the Cancer Institute NSW, as well as individual institutional Ethics Committees. All patients provided written informed consent prior to participating in the trial.

Randomization and Masking

Eligible patients were centrally randomized to perioperative ECF alone (ECF group) or perioperative ECF plus preoperative chemoradiation (chemoradiation group), with registration/consent to trial undertaken blinded to treatment allocation. The 1:1 randomization schedule was generated by the Clinical Trials Centre, using minimization for stratification in the final analysis.

Procedures

The ECF group received three preoperative and three postoperative cycles of ECF chemotherapy. In the chemoradiation arm, patients received two cycles of ECF followed by chemoradiation prior to surgery, and then, following surgery, three further cycles of ECF were administered.

Preoperative and postoperative chemotherapy consisted of epirubicin 50 mg/m^2 intravenously day 1, cisplatin 60 mg/m^2 intravenously day 1, and 5-fluorouracil 200 mg/m^2/day intravenously via 21-day continuous infusion. In some patients, capecitabine 625 mg/m^2 twice daily on days 1–21 was substituted for 5-fluorouracil according to center-specific preferences. This regimen is named ‘ECX’. For simplicity, the text will refer only to ECF.

Chemoradiotherapy was to begin 2–4 weeks after the completion of cycle 2 of induction ECF and consisted of 45 Gy in 25 fractions, 5 days per week for 5 weeks, plus

continuous infusional 5-fluorouracil 200 mg/m^2/day, 7 days per week throughout the entire period of radiotherapy (or capecitabine 825 mg/m^2 twice daily, days 1–5 each week of radiotherapy). Radiotherapy was delivered to the entire stomach, any perigastric tumor extension, and regional lymph nodes using three-dimensional (3D) conformal techniques, intensity-modulated radiotherapy (IMRT), or volumetric-modulated arc radiotherapy (VMAT).

Patients underwent surgery 4–6 weeks following completion of preoperative therapy. Protocol-directed resections included total gastrectomy, subtotal distal gastrectomy, and oesophago-gastrectomy (for gastroesophageal junction tumors). The recommended operation was a D2 gastrectomy where possible, with a minimum approach being a D1+ gastrectomy aiming for complete resection of the primary cancer and its draining nodes.

All patients were reviewed on the first day of each chemotherapy cycle and weekly during chemoradiation, with physical examination, toxicity assessment and performance status assessment, and blood was taken for full blood count and serum biochemistry. Acute toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Patient Follow-Up

Follow-up occurred at 3-month intervals for 2 years, then at 6-month intervals until 5 years. Restaging with computed tomography (CT) of the chest and abdomen was performed at 6 months and 12 months.

Statistical Considerations

The interim analysis of the first 120 patients was planned to examine treatment toxicity, surgical complications, tolerance and delivery of therapy, and pathological response rates by the Independent Data and Safety Monitoring Committee (IDSMC), with recruitment planned to continue provided chemoradiation was deemed to be safe and feasible without clear evidence of lack of improved activity. Additionally, it was planned to report these interim results on safety and feasibility but to maintain the blinding on interim efficacy results. The statistical software package used to perform the analyses was SAS Version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Between September 2009 and June 2014, 120 patients were enrolled in the trial from 51 sites in Australia, New Zealand, Europe, and Canada (recruitment in Europe and Canada only commenced in November 2013). A planned interim analysis of these 120 patients was performed in January 2015 to evaluate key components of the trial relating to safety/toxicity, treatment compliance, accrual, and response rates. The IDSMC determined that no formal criteria to consider trial closure had been met; the committee concluded that recruitment was satisfactory, safety and toxicity were acceptable, and there was no clear evidence of lack of improved efficacy with chemoradiation. The committee recommended that the trial should continue as planned. Following the IDSMC review, selected safety and compliance data unrelated to the primary endpoints of the trial were unblinded to investigators.

Baseline Characteristics

Of the initial 120 patients recruited to the trial, 60 were randomized to the ECF group and 60 to the chemoradiation group. There were no significant differences between the two groups at baseline (Table 1). Twenty-seven percent of patients in both groups were aged $\geq$70 years. In both groups, approximately one-quarter of all tumors were located at the gastroesophageal junction, one-quarter in the lower third of the stomach, and half in the upper and middle thirds of the stomach. Over 80% of tumors in both groups were clinical stage T3/T4 and half were lymph node positive.

Treatment Compliance

Figure 1 and Table 2 show compliance data for the various phases of protocol treatment. The proportion of patients who received all planned cycles of preoperative ECF was 98% in the chemoradiation group (two cycles) and 93% in the ECF group (three cycles), while the proportion of patients who received at least 80% of the planned protocol dose of preoperative ECF was 98% in the chemoradiation group and 92% in the ECF group. For those patients who underwent surgery, the proportion of patients who received all three planned cycles of postoperative ECF was 53% in the chemoradiation group and 65% in the ECF group (difference not statistically significant). There was no difference in the median time from discharge after surgery to commencement of the first cycle of postoperative ECF—6.3 weeks in both groups.

Of the 60 patients in the chemoradiation group, 55 (92%) received chemoradiation. All but one patient (who received 41.4 Gy) completed the full protocol dose of 45 Gy. Fifty-five patients received chemotherapy with radiation, of whom 91% received at least 80% of the planned protocol dose.

The proportion of patients who proceeded to surgery was 85% in the chemoradiation group and 90% in the ECF

TABLE 1 Baseline characteristics

Characteristic	Treatment group	
	Chemotherapy only [$n = 60$]	Chemoradiotherapy [$n = 60$]
Sex		
Male	46 (77)	45 (75)
Female	14 (23)	15 (25)
Age (years)		
<60	19 (32)	25 (42)
60–69	25 (42)	19 (32)
≥70	16 (27)	16 (27)
Tumor site		
Gastroesophageal junction	16 (27)	16 (27)
Lower third	15 (25)	16 (27)
Upper or middle third	29 (48)	28 (47)
T stage		
TX	2 (3)	1 (2)
T1, T2	8 (13)	10 (17)
T3, T4	50 (83)	49 (82)
N stage		
N0	29 (48)	28 (47)
N-positive	31 (52)	32 (53)
Grade		
1	4 (7)	3 (5)
2	17 (28)	15 (25)
3	27 (45)	26 (43)
4	1 (2)	1 (2)
Unknown	11 (18)	15 (25)
Chemotherapy		
ECF	38 (63)	36 (60)
ECX	22 (37)	24 (40)

Data are expressed as *n* (%)

ECF epirubicin, cisplatin and 5-fluorouracil, *ECX* epirubicin, cisplatin and capecitabine

group (Fig. 1; Table 2). Fifteen patients did not proceed to surgery; nine developed tumor progression, two died from chemotherapy-related toxicity, one patient was deconditioned with septicemia following preoperative treatment, one patient developed pulmonary embolus and one patient developed breast cancer. Five patients underwent noncurative surgery; all were found to have extensive disease at the time of laparotomy (mainly peritoneal metastases), resulting in abandonment of surgery (four patients) or palliative surgery (one patient). The median time from completion of preoperative treatment to surgery was 5.7 weeks in the chemoradiation group and 4.9 weeks in the ECF group.

Toxicity

Gastrointestinal and hematologic toxicities predominated as the major (grade 3 or higher) acute toxic effects attributable to perioperative treatment (Table 3). There was no significant difference in overall gastrointestinal toxicity between the two groups, with 30% of patients in the chemoradiation group and 32% of patients in the ECF group experiencing major gastrointestinal toxicity. Similarly, there was no significant difference in overall hematologic toxicity between the two groups (Table 3), with 51.7% of patients in the chemoradiation group and 50% of patients in the ECF group experiencing major hematologic toxicity.

There was no significant difference between the two groups in relation to surgical complications, with approximately 22% of patients in both groups experiencing grade 3 or higher surgical complications (Table 4). Four patients in the chemoradiation group and three in the ECF group developed an anastomotic leak. The breakdown of anastomotic leak according to the type of resection was as follows: total gastrectomy, 2/24 patients in chemoradiation group and 0/19 patients in ECF group; subtotal distal gastrectomy, 1/15 and 3/22; oesophago-gastrectomy, 1/9 and 0/11, respectively. Intra-abdominal sepsis occurred in three patients in the chemoradiation group and four in the ECF group. The breakdown of intra-abdominal sepsis according to type of resection was as follows: total gastrectomy, 1/24 patients in the chemoradiation group and 2/19 patients in the ECF group; subtotal distal gastrectomy, 2/15 versus 2/22; oesophago-gastrectomy, 0/9 versus 0/11. There was no significant difference in the median postoperative length of stay between the two groups: 13 days in the chemoradiation group and 12 days in the ECF group. No postoperative deaths within 30 days of surgery were reported.

Quality Assurance

The trial includes a comprehensive quality assurance program, which includes central review of surgical technique to ensure compliance with protocol guidelines. Following central review, the proportion of patients who underwent a D1+ or D2 dissection was 70% in the chemoradiation group and 76% in the ECF group. Very few patients underwent less than a D1 dissection.

DISCUSSION

Interim results of the TOPGEAR trial demonstrate that preoperative chemoradiation added to perioperative ECF is safe and feasible. This is the largest reported experience describing the use of preoperative chemoradiation for

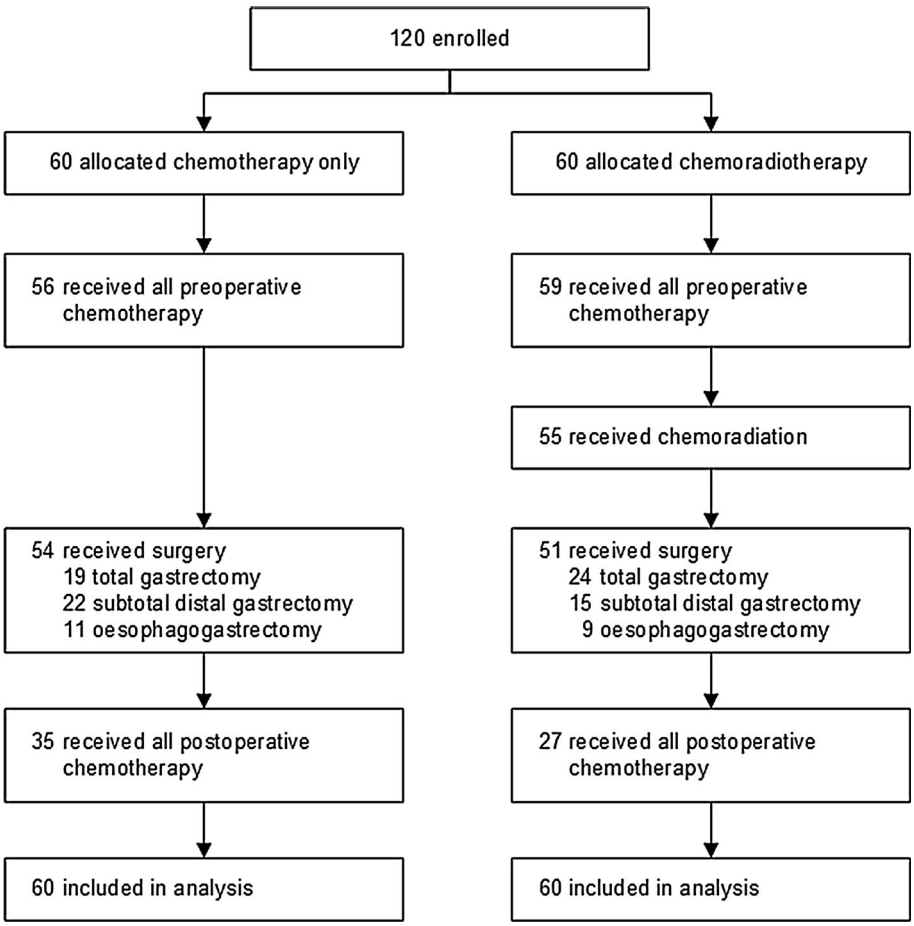

FIG. 1 Trial profile

gastric cancer. Our study demonstrates the advantage of delivering radiotherapy in the preoperative rather than postoperative setting. Ninety-eight percent of patients were able to complete the planned protocol dose of radiotherapy, in contrast to the INT0116 postoperative chemoradiation trial, in which 17% of patients were unable to complete radiotherapy due to treatment-related toxicity.[1] Compliance with perioperative ECF in the present study is similar to that reported in the MAGIC trial, where only half of the patients were able to complete the postoperative component.[2] These figures highlight the benefits of delivering treatment preoperatively when patients are better able to tolerate the toxicities of therapy. Preoperative chemoradiation did not adversely affect surgical compliance. There was no significant difference between the two groups with respect to both the proportion of patients proceeding to surgery and the time to surgery following preoperative treatment. The major reason for patients not proceeding to surgery was disease progression (9 of 15 patients).

The addition of preoperative abdominal irradiation to perioperative ECF did not increase the rates of major hematologic and non-hematologic toxicities, which were similar in the two groups and consistent with those reported in the MAGIC trial for perioperative ECF alone. A major concern during implementation of this trial was the perception (particularly among surgeons) that preoperative radiotherapy could have a deleterious effect on the ability of patients to undergo timely and safe surgery. The high surgical compliance rates in the chemoradiation group indicate that patients do not become overly deconditioned by the preoperative treatment regimen, as is often observed in patients undergoing postoperative radiotherapy. Pleasingly, the results demonstrate that preoperative chemoradiation does not adversely affect surgical morbidity. In particular, the rates of anastomotic leakage and intra-abdominal sepsis were similar in the two arms and were within the range of acceptable surgical standards. Although there have been many reported studies demonstrating the feasibility and safety of preoperative chemoradiation for oesophageal/gastroesophageal junction tumors,[5,7] it is important to note that TOPGEAR is a trial in gastric cancer, for which there is very little information on preoperative chemoradiation. The majority of patients in our study have undergone a total gastrectomy or subtotal distal gastrectomy. The radiation fields for oesophageal cancer are very different to those for gastric cancer, and are

TABLE 2 Treatment compliance

	Treatment group	
	Chemotherapy only [$n = 60$]	Chemoradiotherapy [$n = 60$]
Preoperative chemotherapy		
Received all cycles	56 (93)[a]	59 (98)[b]
Received ≥80% of the planned dose	55 (92)	59 (98)
Chemoradiation		
Received chemoradiation	–	55 (92)
Received 45 Gy (of 56 RT patients)	–	55 (98)
Postoperative chemotherapy		
Received all cycles	35 (65)[c]	27 (53)[d]
Surgery		
Received surgery	54 (90)	51 (85)
No surgery or noncurative surgery	8	12
Total gastrectomy	19	24
Subtotal distal gastrectomy	22	15
Oesophagogastrectomy	11	9
Median time to surgery (weeks)	4.9	5.7

Data are expressed as *n* (%) unless otherwise specified

RT radiotherapy

[a] Three cycles

[b] Two cycles

[c] $n = 53$

[d] $n = 48$

TABLE 3 Gastrointestinal and hematologic toxicity before and after surgery

Toxicity grade 3 or higher	Treatment	
	Chemotherapy only [$n = 60$]	Chemoradiotherapy [$n = 60$]
Gastrointestinal		
Nausea	4 (7)	8 (13)
Vomiting	4 (7)	5 (8)
Dysphagia	5 (8)	6 (10)
Esophagitis	1 (2)	3 (5)
Anorexia	7 (12)	6 (10)
Diarrhea	7 (12)	10 (17)
Overall gastrointestinal	19 (32)	18 (30)
Hematologic		
Neutropenia	24 (40)	27 (45)
Febrile neutropenia	5 (8)	6 (10)
Leukocytes	7 (12)	6 (10)
Anemia	4 (7)	3 (5)
Thrombocytopenia	2 (3)	1 (2)
Overall hematologic	30 (50)	31 (52)

Data are expressed as *n* (%)

TABLE 4 Complications of surgery

Toxicity grade 3 or higher	Treatment	
	Chemotherapy only [$n = 54$]	Chemoradiotherapy [$n = 51$]
Anastomotic leak	3 (6)	4 (8)
Intra-abdominal sepsis	4 (7)	3 (6)
Wound infection	2 (4)	1 (2)
Chest infection	5 (9)	5 (10)
Respiratory failure	0	1 (2)
Cardiac ischemia	1 (2)	0
Overall surgical complications	12 (22)	11 (22)

Data are expressed as *n* (%)

mainly limited to the mediastinum. In contrast, the radiation fields for gastric cancer are much larger and involve irradiation of many critical normal tissues in the abdomen.

While safety and treatment tolerance are reported in this paper, preliminary efficacy results have remained blinded to trial investigators but have been reviewed by the IDSMC to ensure there is not clear evidence of lack of efficacy from preoperative chemoradiation. The Trial Management Committee (who remain blinded) felt that this information could potentially affect trial recruitment if either a perceived high pathological response rate with chemoradiation may encourage clinicians to offer preoperative chemoradiation off study, or a perceived low pathological response rate may discourage clinicians from enrolling patients into the trial. Furthermore, there is strong evidence that pathological response rate does not function as an effective surrogate for survival and should be avoided as an endpoint in clinical trials.[8] Therefore, this information on response may inappropriately lead to some prejudging of the ultimate trial results. Nevertheless, the outcomes on toxicity and feasibility alone are of particular value in reassuring many of the ability to safely deliver the therapy in the ongoing trial.

CONCLUSIONS

The TOPGEAR trial addresses a globally significant question that will help inform future international standards for clinical practice in resectable gastric cancer. Our interim results show that preoperative chemoradiation is

safe and feasible and does not adversely affect surgical morbidity. Upon recommendation from the IDSMC, the trial is continuing as planned, and, when all sites are activated, the TOPGEAR network will comprise approximately 80 centers spanning 15 countries in the Asia–Pacific region, Europe, and North America. Accrual at November 2016 is 318 patients recruited from 60 active sites.

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