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Randomized trial on adjuvant treatment with FOLFIRI followed by docetaxel and cisplatin versus 5-fluorouracil and folinic acid for radically resected gastric cancer

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Background: Some trial have demonstrated a benefit of adjuvant fluoropirimidine with or without platinum compounds compared with surgery alone. ITACA-S study was designed to evaluate whether a sequential treatment of FOLFIRI [irinotecan plus 5-fluorouracil/folinic acid (5-FU/LV)] followed by docetaxel plus cisplatin improves disease-free survival in comparison with 5-FU/LV in patients with radically resected gastric cancer.

Patients and methods: Patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to either FOLFIRI (irinotecan 180 mg/m^2 day 1, LV 100 mg/m^2 as 2 h infusion and 5-FU 400 mg/m^2 as bolus, days 1 and 2 followed by 600 mg/m^2/day as 22 h continuous infusion, q14 for four cycles) followed by docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, q21 for three cycles (sequential arm) or De Gramont regimen (5-FU/LV arm).

Results: From February 2005 to August 2009, 1106 patients were enrolled, and 1100 included in the analysis: 562 in the sequential arm and 538 in the 5-FU/LV arm. With a median follow-up of 57.4 months, 581 patients recurred or died (297 sequential arm and 284 5-FU/LV arm), and 483 died (243 and 240, respectively). No statistically significant difference was detected for both disease-free [hazard ratio (HR) 1.00; 95% confidence interval (CI): 0.85–1.17; $P = 0.974$] and overall survival (OS) (HR 0.98; 95% CI: 0.82–1.18; $P = 0.865$). Five-year disease-free and OS rates were 44.6% and 44.6%, 51.0% and 50.6% in the sequential and 5-FU/LV arm, respectively.

Conclusions: A more intensive regimen failed to show any benefit in disease-free and OS versus monotherapy.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT01640782.

Key words: gastric cancer, adjuvant treatment, adjuvant chemotherapy, randomized clinical trial

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introduction

Gastric cancer (GC) is the second leading cause of cancer mortality in the world. Surgical resection remains the only potentially curative treatment, but recurrence rate of 40%–80% is still high [1].

An individual patient meta-analysis showed that in patients with resected GC, an adjuvant fluorouracil (5-FU)-based chemotherapy provides a statistically significant benefit in terms of overall survival (OS) and disease-free survival (DFS) [2].

During the past decade, different studies have clarified the benefit of a D2 gastrectomy [i.e. systematic removal of the first (perigastric) and second (celiac artery and its branches) level lymph nodes] and that surgical under-treatment can negatively affect survival cancer related [3, 4]. Thus, D2 gastrectomy is now worldwide accepted as standard surgery, while the optimal adjuvant therapy after surgery has not yet been established.

The efficacy of 1-year adjuvant treatment with S-1 compared with surgery alone in stage II–III patients who underwent a D2 gastrectomy was reported by the AGTS-GC Investigators in 2007 [5] and recently confirmed on the basis of 5-year follow-up [6].

Fluoropyrimidine, platinum-based compounds, taxanes, and irinotecan (CPT-11) represent the backbone for most GC treatments. Two-drug platinum or fluoropirimidine schemes have shown similar efficacy and different toxicity profile. Since three-drug combinations—although feasible—are characterized by significant toxicity, an alternative strategy could be the use of sequential chemotherapy in which active and non-cross-resistant drugs are administered at their maximum doses.

Actually, the feasibility of a sequential treatment of CPT-11 plus 5-FU/LV (FOLFIRI) followed by docetaxel plus cisplatin (TXT/CDDP) has been previously demonstrated in the adjuvant setting [7].

Therefore, ITACA-S (Intergroup Trial of Adjuvant Chemotherapy in Adenocarcinoma of the Stomach Trial) study (ClinicalTrials.gov Identifier: NCT01640782) was designed to evaluate whether an adjuvant polychemotherapy with FOLFIRI and TXT/CDDP improves the outcome of patients who underwent radical resection with extended lymph nodes dissection in comparison with a monotherapy with 5-FU/LV.

methods

study design

This was a multicenter, randomized, open-label, active-controlled, of superiority, phase III trial. Patients were randomly assigned to one of the two adjuvant chemotherapy regimens, using a centrally managed, computer-generated, permuted-block randomization scheme, with a 1:1 ratio, stratified by center and nodal involvement [no positive nodes (pN−) versus ≥1 positive node (pN+)].

An independent data monitoring committee, which annually met to review accrual, safety, and efficacy, monitored the study. No formal stopping rules were adopted.

The Istituto di Ricerche Farmacologiche 'Mario Negri' played the role of not-for-profit sponsor. Eleven oncological groups collaborated with the sponsor in the planning and management of the study.

eligibility criteria

The inclusion criteria were: a histologically proven diagnosis of adenocarcinoma of the stomach or gastroesophageal junction; radical resection of tumor no more than 8 weeks before the randomization without gross or microscopic evidence of residual disease; pN+ or pN− patients with pT2b-3–4 according to the International Union Against Cancer (UICC) [8]; Eastern Cooperative Oncology Group performance status (ECOG-PS) < 2; age ≤ 75 years; no previous malignancies other than superficial skin cancer or *in situ* cervical carcinoma; no previous chemotherapy or radiotherapy; and no evidence of abnormal hepatic, renal, or cardiac function.

In each centre, study protocol had to be approved by institutional review board and a written informed consent of subjects had to be given before any study-related activities were carried out.

surgery

Surgical procedures were not standardized among participating centers. The minimum surgical recommendations included total or subtotal gastrectomy with negative resection margins with at least a D1 (i.e. lymphadenectomy of the perigastric lymph nodes) dissection.

treatment plan

In the experimental sequential arm, treatment consisted in CPT-11 180 mg/m^2 1 h infusion day 1, LV 100 mg/m^2 2 h infusion days 1–2 and 5-FU 400 mg/m^2 as bolus followed by daily 22 h infusion of 600 mg/m^2, q14 for four cycles and after 3 weeks docetaxel 75 mg/m^2 1 h infusion day 1, followed by cisplatin 75 mg/m^2 day 1, q 21; for three cycles. Dexamethasone was recommended before, 12 and 24 h after docetaxel.

In the control 5-FU/LV group, according to De Gramont regimen, patients were given LV 100 mg/m^2 2 h infusion days 1–2 and 5-FU 400 mg/m^2 as bolus followed by daily 22 h infusion of 600 mg/m^2 every 14 days for nine cycles.

Pre-specified dose modifications were done for patients who experienced hematologic and non-hematologic toxicities. Growth factors were permitted for prolonged or complicated severe neutropenia.

assessments

Adjuvant baseline assessment included a history taking: physical examination, routine hematologic/biochemical tests, electrocardiogram, pregnancy test, CEA and CA-19.9, abdominal ultrasonography and/or computed tomography (CT), chest X-ray, and bone scan.

Before each chemotherapy cycle, physical examination and laboratory tests had to be repeated. At the end of chemotherapy treatment, physical examination, vital signs, laboratory tests, CT scan, and tumor markers were required. Follow-up visits were done every 4 months for the first 3 years; then at 8-month intervals up to the fifth year, and thereafter at investigator's discretion. Follow-up consisted of a physical examination, routine laboratory tests, abdominal CT scan, gastroscopy, and chest X-ray. Site and date of the first recurrence and, if patient died, the date of death were recorded. Disease recurrence (loco-regional and/or metastatic disease) was determined by clinical, radiologic, and, whenever possible, histological examination.

All adverse events were graded according the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), version 2.0.

statistical methods

The primary end point was DFS; secondary outcomes were OS, treatment compliance, and tolerability. We defined DFS as the time from randomization to first appearance of recurrence/death from any cause; patients known to be alive and without disease at the time of analysis were censored at their last follow-up. OS was defined as the time from randomization to death from any cause; patients known to be alive at the time of analysis were censored at their last follow-up.

Expecting a 3-year DFS around 50% in the5-FU/LV group, we set an accrual target of ∼1100 patients to observe 636 recurrences/deaths. This number of events was required to detect an absolute DFS difference of 7%,

corresponding to a hazard ratio (HR) of 0.80 with 80% power at 5% significance level. Both accrual and follow-up lengths were 3 years.

We compared the Kaplan–Meier curves for survival with the Mantel–Cox version of log-rank test. A Cox proportional hazards model was used to estimate treatment effect adjusted for prognostic factors, such as stage, number of positive nodes, and tumor site. The differences in relative effect size in selected subgroups were described by forest plots of HR and relative confidence interval (CI) in each level of factors considered, and tested with the χ^2 test for interaction.

To test for differences in tolerability, we used a χ^2 test for trend.

Analyses were done by intention to treat, except for those of compliance and tolerability carried out considering patients in the arm of the treatment they actually received. All reported *P*-values are two-sided, and CIs are at 95% level (95% CIs).

Analyses were carried out using SAS statistical software, version 9.1.3 (SAS Institute Inc., Cary, NC).

results

From February 2005 to August 2009, 1106 patients were enrolled by 104 centers. Six patients, five with metastatic disease and one randomized by mistake, were excluded. Therefore, the analysis was carried out on 1100 patients, 562 in the sequential arm and 538 in the 5-FU/LV arm (supplementary Figure S1, available at *Annals of Oncology* online).

As shown in supplementary Table S2, available at *Annals of Oncology* online, patient and tumor characteristics were well balanced between the two treatment groups.

surgery

A D1 lymphadenectomy was carried out in 25% of patients, while most patients undergone a D2 lymphadenectomy (72%). The median number of lymph nodes removed per patient was 27 in both arms. Fifty-five percent of the patients underwent a total gastrectomy.

compliance

Twenty-eight patients, 12 in the sequential and 16 in the 5-FU/LV arm, did not start chemotherapy, mainly due to treatment refusal. Further two and four patients, respectively, crossed treatment and for the analysis of compliance and toxicity were analyzed in the arm of treatment they actually received.

Of the 520 patients who started 5-FU/LV, 450 (86.5%) completed the treatment, 70 (13.5%) stopped it because of toxicity ($n = 30$), relapse/death ($n = 20$), or other reasons ($n = 20$). Among patients who completed treatment, a dose reduction and/or a time modification was required in 265 patients (58.9%).

Out of 552 who started the sequential treatment, 421 (76.3%) completed it, 131 (23.7%) stopped chemotherapy because of toxicity ($n = 83$), relapse/death ($n = 11$), refusal ($n = 29$), or other reasons ($n = 8$). Only 92 patients (16.7%) completed treatment without time and dose changes.

The median number of cycles administered was nine, ranging from one to nine, and seven, ranging from one to seven, in 5-FU/LV and sequential treatment, respectively.

toxicity

The observed toxic effects are summarized in supplementary Table S3, available at *Annals of Oncology* online. As expected, the polychemotherapy was less tolerated, with a more frequent grade 3–4 episodes for almost all toxicities. Overall, a grade 3–4 toxic episode (also grade 2 for neurotoxicity) was reported at least once in 361 (65.4%) and 99 (19.0%) patients in the sequential and 5-FU/LV arm, respectively. Hematological and gastrointestinal (i.e. nausea, vomiting and diarrhea) toxicities predominated. The most common hematological toxicity was neutropenia. Three toxic deaths occurred: one in the 5-FU/LV arm for mucositis and two in the sequential arm due to stupor condition and diarrhea/vomiting.

disease-free and overall survival

On 21 January 2013, the median follow-up was 57.4 months in the 5-FU/LV and 56.0 months in the sequential arm. Since we observed 91% of the target events for DFS and 96% of the patients recurred/died or were followed for more than 3 years, we decided to perform the final analysis. Given the data observed, both under original hypothesis and current trend, the probability to reach a statistically significant result at the target number of events was <0.0001.

Recurrence was observed in 518 patients: 262 (46.6%) in the sequential arm and 256 (47.6%) in the 5-FU/LV arm, without difference in the pattern of first sign of recurrence. In both arms, most patients had a metastatic disease (79.8% in the sequential and 83.6% in the 5-FU/LV arm), while loco-regional recurrence occurred in 10.4% and 9.4% patients, respectively. Twenty-three (8.8%) patients in the sequential and 18 (7.0%) in the 5-FU/LV arm had both loco-regional recurrence and metastatic disease.

A total of 483 patients died (243 in the sequential arm and 240 in the 5-FU/LV arm) and 581 patients recurred or died: 297 (52.8%) and 284 (52.8%), respectively.

Both DFS [HR for recurrence/death 1.00; 95% CI 0.85–1.17; $P = 0.974$ (supplementary Figure S4, available at *Annals of Oncology* online)], and OS [HR for death 0.98; 95% CI 0.82–1.18; $P = 0.865$ (supplementary Figure S5, available at *Annals of Oncology* online)] were overlapping between arms.

Adjustment for stratification factors gave an HR for recurrence/death of 0.98 (95% CI 0.83–1.16; $P = 0.805$) and an HR of death of 0.99 (95% CI 0.82–1.18; $P = 0.877$), as shown in supplementary Table S6, available at *Annals of Oncology* online.

Five-year DFS rates were 44.6% (95% CI 38.9–50.3) among patients in the sequential and 44.6% (95% CI 42.7–46.6) among those in the 5-FU/LV group. Five-year OS rates were 51.0% (95% CI 44.8–56.8) and 50.6% (95% CI 48.3–53.1), respectively.

The interaction analyses (supplementary Figures S7 and S8, available at *Annals of Oncology* online) did not show any interaction for all considered variables both for OS and DFS.

discussion

Our randomized study failed to show any statistically significant benefit in terms of both DFS and OS in patients with radically resected GC receiving an adjuvant treatment with FOLFIRI followed by docetaxel and cisplatin versus a 5-FU/LV regimen.

A recent Japanese study compared the following four different adjuvant regimens: UFT alone, S-1 alone, or sequential therapy with paclitaxel followed by either UFT or S-1. The trial was

aimed at comparing UFT with S-1, and both single agents with a sequential, taxane-based regimen. It failed to show a statistically significant difference in DFS of the sequential arms when compared with single-agent fluoropyrimidine arms (HR = 0.92; CI, 0.80–1.07, $P = 0.273$). Moreover, UFT-based chemotherapy was clearly less effective than S-1-based one. Therefore, a sequential polychemotherapy does not seem to improve GC patient outcome in the adjuvant setting [9].

Since fluoropyrimidine and platinum salts have synergistic activity, their combination may hopefully be more effective than a single-agent regimen; similarly, the CLASSIC study was designed to compare the efficacy of adjuvant capecitabine plus oxaliplatin (XELOX regimen) versus surgery alone in stage II or III GC patients [10]. At 5 years, DFS was 68% versus 53% (HR: 0.58; 95% CI 0.47–0.72; $P < 0.0001$). Five-year OS rates were 78% in the XELOX group and 69% in the surgery alone group (HR: 0.66; 95% CI 0.51–0.85; $P = 0.002$). However, the greater limit of this study is that the control arm consisted in surgery alone that is considered no more appropriate, since the benefits of adjuvant chemotherapy were clearly demonstrated. Indeed, the ongoing POTENT study is moving along this line. This is a randomized trial that started enrollment in early 2013 and randomizes patients to receive oxaliplatin and S-1 for six cycles or S-1 for 1 year after surgery, having OS as the primary end point.

Another issue is that in our trial, a large proportion of patients (75%) underwent at least a D2 lymphadenectomy and the study confirmed the high survival rates observed in previous studies in the adjuvant setting [11–13]. Moreover, local recurrence developed in only 10% is likely the result of more extensively lymph node dissection.

The frailty of GC patients after surgery combined with toxicity of adjuvant polychemotherapy could explain the poor compliance to treatment and the lack of benefit. In the present study, sequential treatment was completed in 76.3% of patients but, burdened with more frequent grade 3–4 hematologic and gastrointestinal toxicities, only 16.7% completed treatment without time and dose modifications. However, for this reason, we believe that the treatment with FU/LV is enough and should be a valid option in resected patients; further attempts to dose intensification will not increase the benefit of adjuvant therapy after radical gastric resection. Different is the role of polychemotherapy in preoperative phase and ongoing studies such as CRITICS should give a response.

If the capability to improve patient outcome with current adjuvant therapies seems modest, at least in western countries, it is possible to pursue different complementary research strategies. First of all, a better patient selection according to molecular tumor characteristics. ToGA study [14] showed the superiority of the combination of trastuzumab with a fluoropyrimidine (5-FU or capecitabine) plus cisplatin every 3 weeks compared with chemotherapy alone in terms of OS in patients with advanced GC and HER2 protein overexpression. The assessment of trastuzumab or novel anti-HER2 drugs in the perioperative and adjuvant setting seems as a challenging perspective.

Different modalities of scheduling and combination therapies could further improve the prognosis of GC patients. Neoadjuvant chemotherapy has recently received attention in an attempt to prolong survival. The available data indicate that neoadjuvant chemotherapy is feasible and does not increase adjuvant morbidity and mortality. In particular, several small phase II trials on different neoadjuvant cisplatin-based chemotherapy regimens reported response rates between 40% and 60% and R0 resection rates up to 80% [15, 16].

MAGIC trial [17] was the first study that demonstrated a benefit of perioperative chemotherapy. Five-year survival was 36% in the perioperative chemotherapy versus 23% in the surgery alone group, making the perioperative chemotherapy the standard care in UK.

Although chemoradiotherapy in the adjuvant setting improves survival based on the results of the INT-0116, the role of this approach after a D2 dissection needs to be further investigated [18]. This trial demonstrated that adjuvant radiotherapy plus 5-FU chemotherapy significantly improves recurrence-free survival and OS of patients with locally advanced adenocarcinoma of the stomach or gastroesophageal junction. The surgical procedure was considered inadequate since only 10% of patients had D2 lymph nodes dissection and chemoradiotherapy treatment reported a high rate of acute toxicity probably due to the large field of irradiation and to the radiotherapy technique used. Moreover, in an update of INT-0116, a subset analysis showed no differences in OS and DFS of patients who underwent a D2 nodal dissection compared with other patients [19]. Following the promising results of the INT-0116 trial, the CALGB 80101 aimed at assessing whether replacing 5-FU/LV with Epirubicin, Cisplatin, and 5-FU (ECF regimen) improve OS [20]. There was no significant benefit from adding this polychemotherapy regimen to standard 5-FU/LV chemoradiation in terms of OS. Recently, a phase III trial conducted in Korea did not show a survival benefit for adjuvant chemoradiation therapy versus chemotherapy, following a D2 surgery [21].

Up-to-date, the use of adjuvant chemotherapy is mainly supported by positive results of two phase III trials in which surgery alone was the control arm, since trials comparing polychemotherapy or chemoradiotherapy versus an active control failed to show any benefit for patients [6, 10, 20, 21].

Despite this great number of trials, due to the strong limits related to the differences in population characteristics and surgical techniques, any attempt to an indirect comparison exercise appears inappropriate.

Therefore, FU/LV can be considered the standard treatment in patients radically operated with D2 dissection.

Studies evaluating either HER2-oriented approaches or adjuvant versus neoadjuvant chemotherapy with or without radiotherapy are highly warranted.

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disclosure

The authors have declared no conflicts of interest.

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appendix

ITACA-S Study Group

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