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Feasibility of Sequential Therapy with FOLFIRI Followed by Docetaxel/Cisplatin in Patients with Radically Resected Gastric Adenocarcinoma

A Randomized Phase III Trial

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Key Words
Adjuvant chemotherapy · Docetaxel · Gastric cancer · Irinotecan

Abstract
Objective: Combination therapies of fluorouracil (FU) with irinotecan (CPT-11) and docetaxel plus cisplatin have been proven to be active in metastatic gastric cancer. In this paper, we present the results of a phase III trial in which these two combinations given sequentially were compared to mitomycin C (MMC) monochemotherapy in an adjuvant setting. ***Methods:*** 169 patients with radically resected gastric cancer were randomized to receive CPT-11 (180 mg/m^2 day 1), leucovorin (100 mg/m^2 days 1–2), FU (400–600 mg/m^2 days 1–2, q 14; for four cycles; FOLFIRI regimen), followed by docetaxel (85 mg/m^2 day 1), cisplatin (75 mg/m^2 day 1, q 21; for three cycles; arm A), or MMC (8 mg/m^2 days 1–2 as 2-hour infusion, q 42; for four cycles; arm B). All patients had histologically confirmed gastric carcinoma with nodal positivity or pT3/4. A total of 166 patients (85 in arm A and 81 in arm B) were treated. Adjuvant treatment was completed in 76% of the patients in arm A and in 70% of the patients in arm B. The main grade 3/4 side effects recorded were neutropenia in 35%, with only 1 febrile patient, and diarrhea in 11% in arm A, and thrombocytopenia in 10% and neutropenia in 7% in arm B. The FOLFIRI regimen and docetaxel/cisplatin given in sequence was well tolerated and feasible in adjuvant setting. This sequence treatment currently represents the experimental arm of an ongoing multicenter trial.

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Introduction

Gastric cancer still represents the fourth leading cause of cancer mortality worldwide [1]. The current 5-year survival rate in Europe is approximately 30–40%, a figure that has improved little over the last decade [2]. Adjuvant chemotherapy after radical resection has largely been evaluated over the past 10–15 years without drawing any definite conclusions. All previous randomized trials exploring adjuvant therapy had inadequate sample sizes to validate objective responses, and patient entry criteria differed among the studies. Several meta-analyses were performed, and the results reported a small significant benefit for chemotherapy-treated patients with hazard ratios ranging from 0.72 to 0.84 [3–6]. These conclusions have been drawn with old drug combinations, and currently no regimen is recognized and accepted as standard [7].

Irinotecan (CPT-11) is a cytotoxic agent with promising activity in gastric cancer when combined with cisplatin or fluorouracil (FU) [8–10]. Biweekly FU and leucovorin treatment in combination with CPT-11 achieves response rates of 40% and a median survival of 11.3 months in metastatic gastric cancer [11]. In addition, a randomized phase III trial comparing CPT-11 plus infusional FU versus cisplatin plus FU has recently been published. FU/CPT-11 has a better safety profile than cisplatin/FU, with less hematologic, renal and neurologic toxicity and less stomatitis [12]. This combination represents an alternative first-line treatment option without cisplatin [13].

Docetaxel and paclitaxel have also demonstrated activity in advanced gastric cancer [14]. The triplet combination consisting of docetaxel, cisplatin and FU has been reported effective in terms of objective response and overall survival (OS) rates when compared to a doublet combination with cisplatin and FU or with docetaxel and cisplatin, but more grade 3–4 adverse events were reported. In particular, hematological toxicity was the main side effect occurring in over 70% of patients receiving the triplet combination [15, 16].

In the Japanese literature, positive survival results were often reported using postoperative adjuvant chemotherapy based mainly on mitomycin C (MMC) regimens [17]. These positive results were confirmed by a Spanish group in randomized trials, supporting the use of adjuvant MMC versus no further treatment [18, 19].

This study was initially designed to compare disease-free survival (DFS) in patients treated with two regimens given in sequence, CPT-11/FU (FOLFIRI) followed by docetaxel/cisplatin, and DFS in patients treated with an MMC regimen after radical gastrectomy for adenocarcinoma of the stomach or gastroesophageal junction. The sequence was chosen in order to minimize the toxicity profile of the drug combinations, considering the different side effects related to the FOLFIRI regimen and those related to docetaxel/cisplatin.

This report describes the preliminary analysis performed. The results of this study prompt us to perform a larger randomized trial involving all Italian multicenter groups.

Patients and Methods

Patients

Patients with histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction treated with radical resection were enrolled in this trial. Surgical resection was defined as radical when no microscopic residue was left in the resection margins (R0). All patients had at least one of the following unfavorable characteristics: serosal invasion (pT3); extension to adjacent organs (T4) or involvement of regional lymph nodes (pN+). Patients had to have: ECOG performance status 0–2 (in patients >70 years an ECOG performance status of 0–1 was required); age between 18 and 75 years; adequate hematological (neutrophils $>2 \times 10^9$/l; platelets $<150 \times 10^9$/l), hepatic (bilirubin <25 μmol/l, and aspartate aminotransferase and alkaline phosphatase <5× upper limit of normal), renal (creatinine <130 μmol/l) and cardiac function; recovery from acute effects of surgery, and absence of complications within 8 weeks from surgery. The exclusion criteria included the presence of other systemic diseases limiting patient survival and the presence of other cured neoplasms with no evidence of disease in the last 5 years. The patients were not included if they were pregnant or lactating. Contraceptive measures were required for patients with reproductive potential. The study was conducted according to the Good Clinical Practice Rules and the Declaration of Helsinki. Written informed consent was required ab initio. The study and all current amendments were approved by the Ethics Committees of all the participating centers.

Randomization and Stratification

Eligible patients were registered at the ITMO (Italian Trial in Medical Oncology) Scientific Office by fax. Randomization was stratified according to the following patient characteristics: lymphadenectomy dissection (D1 vs. D2–D3) and the number of lymph nodes involved (N0–1 vs. N2–N3). Permuted-block randomization lists were prepared for each center.

Surgical Procedures

Lymph node dissection included at least the first level, although a second-level dissection, according the Japanese Research Society for Gastric Cancer, was recommended. This procedure entails the resection of all perigastric, celiac, splenic, hepatic artery and cardial nodes, depending on the location of the tumor in the stomach.

Treatment Plan

In this prospective phase III trial, patients after stratification were randomized to receive polychemotherapy (arm A) or mono-

chemotherapy (arm B). The polychemotherapy consisted of CPT11 (180 mg/m^2) delivered as a 1-hour infusion only on day 1, folinic acid (100 mg/m^2) as a 2-hour infusion, a 400-mg/m^2 FU bolus and a 22-hour continuous infusion (600 mg/m^2 on days 1 and 2) of FU (FOLFIRI regimen) for four cycles, followed by docetaxel 85 mg/m^2 delivered by 1-hour infusion and 75 mg/m^2 cisplatin for three cycles every 21 days. Premedication with dexamethasone was recommended before and 12 and 24 h after the docetaxel infusion. The arm B treatment consisted of MMC at a dosage of 10 mg/m^2 every 4 weeks on days 1 and 2 for a total of six cycles. After the first 13 patients, this program was amended, and MMC dosage was reduced to 8 mg/m^2 as a 2-hour infusion every 42 days for four cycles.

Patient Follow-Up

The baseline assessment included a complete medical history and physical examination, a complete blood count (CBC), and renal and hepatic function tests within 1 week before protocol inclusion. An abdominal ultrasound or computed tomography scan and a chest X-ray were required 1 month before or after surgery. Before each chemotherapy cycle, CBC and renal tests were repeated. All adverse events were graded using the Common Toxicity Criteria of the National Cancer Institute (CTC-NCI).

Follow-up of both groups (at 4-month intervals for 5 years, and yearly thereafter) consisted of a complete physical examination, CBC, liver function tests, CEA level and abdominal ultrasonography or CT scan. An upper endoscopy was required every 8 months. Disease recurrence was ascertained by clinical, radiological and, whenever feasible, histological examination.

Statistical Methods

The study was initially designed to compare the DFS of the two treatment arms, calculated as the time between randomization and the occurrence of tumor relapse, either locoregional or distant. OS was also investigated. Survival curves were calculated by the Kaplan-Meier method, and the log rank test was used to compare the curves between the two trial arms.

Using Friedman's formula for sample size calculation, we estimated that the number of tumor relapses recorded during the trial had to be 403 under the following assumptions: 10% increase in 5-year DFS, from an anticipated 40% in the MMC arm to 50% in the sequential treatment arm (a difference corresponding to a hazard ratio, HR, of 0.76, or a 24% relative rate reduction), 80% power to detect the above delta with a 2-sided log rank test at 5% significance level. Two different kinds of Bayesian analysis, both aimed at assessing robustness of these preliminary results, were carried out. The first, proposed by Fayers et al. [20], was based on estimating the (posterior) probability of favorable experimental treatment effects (HR <1) or an effect at least equal to the target (HR ≤0.76), conditional on observed data. Calculations were carried out assuming a log-normal distribution of the estimated HR and a 'skeptical' prior (5% prior probability of HR ≤0.76). The second approach was based on predictive probability, referring to the probability of concluding in favor of one of the treatments if the trial were run to completion. Further statistical details can be found at the MD Anderson Cancer Center Biostatistics Unit website (http://biostatistics.mdanderson.org). In this study, the same prior γ distribution was assumed for both trial arms, and its parameters were chosen in such a way that the mean was equal to the event rate expected in the control arm and the variance was such to make an event rate equal or greater than the target level assumed in the experimental arm unlikely (5% probability). Adverse events were monitored continuously during treatment and for 28 days after the last study drug administration.

The intensity of adverse events and laboratory parameters was graded according to CTC-NCI for Adverse Events (version 3.0).

Table 1. Main patient and disease characteristics in both treatment arms

	Arm A (n = 85) n (%)	Arm B (n = 81) n (%)
Age		
<70 years	75 (76.5)	73 (86.4)
≥70 years	10 (11.8)	8 (9.8)
Males/females	71%/29%	68%/32%
Tumor site		
Cardia/fundus	10 (12.3)/10 (12.3)	30 (18.1)/17 (10.2)
Antrus/pilorus	32 (39.5)/13 (16.0)	70 (42.2)/23 (13.9)
Corpus	26 (32.1)	54 (32.5)
Histologic type		
Diffuse	19 (23.5)	35 (21.1)
Intestinal	22 (27.2)	45 (27.1)
Mixed	3 (3.7)	9 (5.4)
NOS	29 (35.8)	57 (34.3)
Other	8 (9.9)	20 (12.0)
Tumor stage		
pT_{1-2}	37 (43.5)	29 (35.8)
pT_{3-4}	48 (56.5)	52 (64.2)
pN_0	7 (8.2)	6 (7.4)
pN_1	44 (51.8)	50 (61.7)
pN_2	23 (27.1)	19 (23.4)
pN_3	11 (12.9)	6 (7.4)
Node dissection		
D1/D2–3	19 (22.3)/66 (77)	19 (23.4)/62 (76)
Number of nodes analyzed		
<15	11 (12.9)	13 (16.1)
15–30	49 (57.6)	38 (46.9)
>30	24 (28.2)	30 (37.0)
Median	24	26

Results

Between June 2000 and June 2004, 169 patients were included by 23 Italian institutions. Three patients dropped out before starting treatment. Therefore, the safety population comprised 166 patients of whom 85 received FOLFIRI followed by docetaxel/cisplatin and 81 received MMC. Table 1 shows the main patient characteristics; the two arms were well balanced overall, except for a slightly higher prevalence of pN2–pN3 cases in arm A. Notably,

Table 2. Side effects reported in arm A (NCI-CTC)

	Patients, n (%)			
	grade 1	grade 2	grade 3	grade 4
Diarrhea				
CPT11+FU/FA	16 (18.8)	9 (10.5)	5 (5.8)	1
CDDP+TXT	7 (8.2)	11 (12.9)	4 (4.7)	–
Overall	15 (17.6)	16 (18.8)	9 (10.5)	1
Leukopenia				
CPT11+FU/FA	14 (16.4)	8 (9.4)	4 (4.7)	1
CDDP+TXT	5 (5.8)	9 (10.5)	8 (9.4)	2 (2.3)
Overall	10 (11.7)	10 (11.7)	10 (11.7)	3 (3.5)
Neutropenia				
CPT11+FU/FA	9 (10.5)	18 (21.1)	10 (11.7)	8 (9.4)
CDDP+TXT	4 (4.7)	5 (5.8)	4 (4.7)	16 (18.8)
Overall	7 (8.2)	13 (15.2)	8 (9.4)	22 (25.8)
Mucositis				
CPT11+FU/FA	9 (10.5)	6 (7)	4 (4.7)	–
CDDP+TXT	8 (9.4)	4 (4.7)	3 (3.5)	–
Overall	13 (15.2)	7 (8.2)	7 (8.2)	–
Alopecia				
CPT11+FU/FA	4 (4.7)	7 (8.2)	3 (3.5)	–
CDDP+TXT	–	11 (12.9)	6 (7)	1
Overall	2 (2.3)	14 (16.4)	6 (7)	1

CDDP = Cisplatin; TXT = docetaxel.

Table 3. Side effects reported in arm B (NCI-CTC)

	Patients, n (%)			
	grade 1	grade 2	grade 3	grade 4
Diarrhea				
Before (n = 13)	2 (15.3)	–	1	1
After (n = 68)	8 (11.7)	1	–	–
Leukopenia				
Before (n = 13)	1	3 (23)	2 (15.3)	1
After (n = 68)	10 (14.7)	7 (10.2)	2 (2.9)	–
Neutropenia				
Before (n = 13)	–	1	5 (38)	1
After (n = 68)	5 (7.3)	8 (11.7)	5 (7.3)	1
Thrombocytopenia				
Before (n = 13)	1	3 (23)	5 (38)	2 (15.3)
After (n = 68)	6 (8.8)	3 (4.4)	6 (8.8)	1
Nausea				
Before (n = 13)	4 (30)	1	3 (23)	1
After (n = 68)	17 (25)	3 (4.4)	–	–

a high percentage of cases (85% overall) had 15 or more lymph nodes sampled for pathologic assessment (median number: 25), compatible with the high frequency (77%) of D2–3 dissections.

Sequential treatment was completed in 65 (76%) patients. In 20 patients (23.3%), treatment was discontinued. The reasons for discontinuation were: adverse events (7%), consent withdrawn (7%) and progressive disease (3.5%). Two patients died during treatment: 1 due to gastrointestinal bleeding and the other committed suicide. The intended dose was administered in 56 cases (66%) during the FOLFIRI and in 44 cases (59%) during the docetaxel/cisplatin treatment, whereas 23% of the patients received FOLFIRI and 28.2% received docetaxel/cisplatin with at least one dose reduction. A delay of at least one cycle was documented in 45% of the patients during FOLFIRI and 21% during docetaxel/cisplatin.

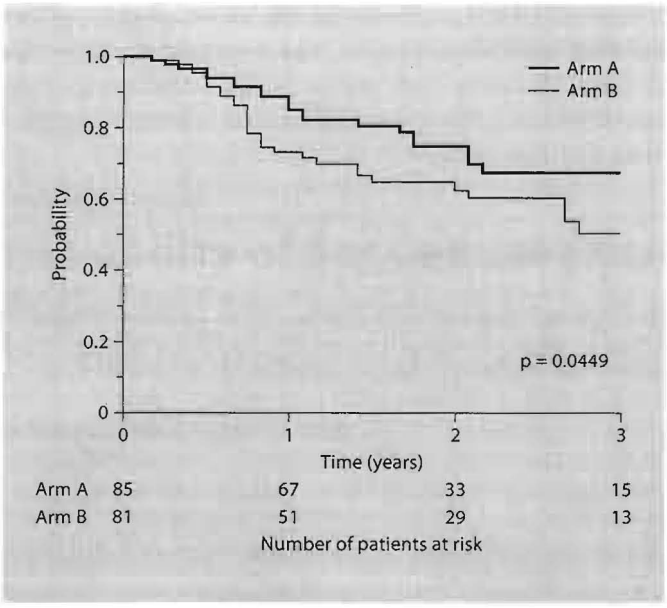
In arm B, 13 patients were treated before the protocol amendment. Of these, only 5 (39%) completed therapy and only 1 received full-dose treatment. After the amendment, 68 patients were treated for a median of four cycles. Fifty-seven patients (83%) completed therapy and 49 (72%) received full-dose treatment. The reasons for discontinuation were: adverse events (10%), progressive disease (9%) or consent withdrawn (1%).

The main side effects observed during the study are reported in table 2 for arm A and in table 3 for arm B. Overall, grade 3–4 side effects were recorded in 47 (55%) patients in arm A and in 22 (27%) in arm B. The main grade 3/4 toxicities in arm A were: neutropenia (35%), diarrhea (11%) and grade 3 vomiting (14%). In arm B the main grade 3/4 toxicities were: thrombocytopenia (10%) and neutropenia (7%). Complicated neutropenia (febrile neutropenia) was reported in 5 (6%) patients, with 4 occurring during docetaxel/cisplatin. No episode of febrile neutropenia was reported in arm B.

Hemolytic syndrome was recorded in 2 patients in arm B receiving MMC before the protocol amendment.

After a median follow-up of 29 months, 49 deaths (21 in arm A and 28 in arm B), and 53 tumor relapses (21 in arm A and 32 in arm B) were recorded. DFS and OS curves in the two trial arms are shown in figures 1 and 2, respectively. Survival rates were more favorable in arm A than in arm B. Three-year estimates were 67.4 versus 50.2% for DFS ($p = 0.0449$) and 73.5 versus 62.4% for OS ($p = 0.1634$), corresponding to a 35% relative risk reduction of disease relapse and a 30% relative mortality reduction.

A statistically significant difference in DFS, the primary study end point for efficacy, was achieved in an unplanned interim analysis. We checked the robustness of the mentioned result with the above-mentioned, two



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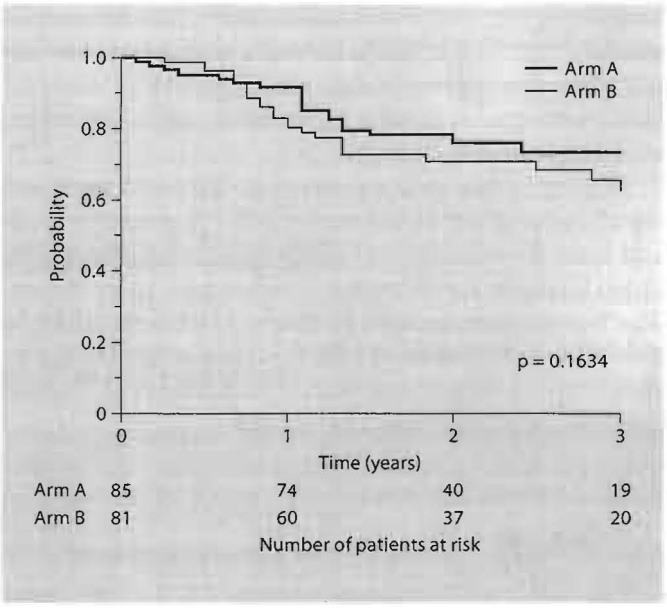

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Fig. 1, 2. DFS (**1**) and OS (**2**) according to treatment arm.

Bayesian analyses, which revealed that the significant result could not be considered as conclusive (low posterior probability of an experimental treatment effect at least equal to the target: HR ≤ 0.76, $p = 0.186$), but also that the experimental treatment used in arm A is likely effective (high posterior probability of a favorable experimental treatment effect: HR <1, $p = 0.851$, and high predictive probability of a significant result should the trial be run to completion, $p = 0.92$).

Discussion

The novelty of the present study is the sequential use of the FOLFIRI regimen followed by docetaxel/cisplatin as adjuvant treatment in radically resected gastric carcinoma.

The combination of docetaxel/cisplatin/FU given in the metastatic phase significantly decreases the time to progression, and improves OS and response compared to cisplatin/FU, although with an expected increase in side effects (grade 3–4 neutropenia: 82%) [16]. The feasibility of efficient treatment in the adjuvant phase represents a main problem. Indeed, in many negative randomized trials, poor compliance to therapy might represent the principal reason for the lack of effectiveness [21, 22].

The combinations of FOLFIRI and docetaxel/cisplatin appear feasible with different toxicity profiles. The sequential treatment was well tolerated, which is reflected by the fact that the regimen was completed in 76% of the patients, and full-dose cycles were administered in >60% of the patients. Two sequential regimens induced grade 3–4 neutropenia in 32% (febrile neutropenia: 6%) and grade 3–4 diarrhea in 12% of the patients treated. This limited toxicity can be explained by the fact that the two regimens have a different toxicity profile as well as a relatively short period of drug treatment.

In a previously published study, we have reported the feasibility of sequential administration of etoposide, cisplatin and doxorubicin (EAP) followed by FU/leucovorin in patients after D2 gastrectomy. Although this analysis failed to reach statistical significance in terms of OS compared to surgery alone, we have documented a good safety profile of the chemotherapy regimens which were sequentially administered [23, 24].

In addition, noncompliance was shown for cisplatin/FU therapy, since only 62% of the patients completed treatment in a French study, which documented a small nonsignificant benefit [25].

In both studies, the 5-year OS of the control arm was significantly better than that expected which was also used for the statistical calculations. Moreover, the trials were powered to detect a 15% increase in survival. The fact that the results did not reach statistical significance is therefore not surprising.

The original aim of the randomized trial was to evaluate the efficacy (in terms of DFS) of a new therapeutic approach consisting of two sequential regimens given in patients with gastric cancer subjected to radical resection and adequate lymphadenectomy.

Regarding the efficacy analysis, since the statistical significance of the difference in DFS (the primary study end point for efficacy) was achieved in an unplanned interim analysis, no definitive conclusions can be drawn. The 3-year estimates were 67.4 versus 50.2% for DFS ($p = 0.0449$) and 73.5 versus 62.4% for OS ($p = 0.1634$), corresponding to a relative risk reduction of relapse of 35% and a relative mortality reduction of 30%.

To confirm the efficacy of the above-mentioned sequential treatment regimen, the principal investigators decided to start a multicenter national trial comparing our sequential therapy to a standard reference regimen with FU/leucovorin.

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