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Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study)

C. Pinto[1]*, F. Di Fabio[1], S. Siena[2], S. Cascinu[3], F. L. Rojas Llimpe[1], C. Ceccarelli[4], V. Mutri[1], L. Giannetta[2], S. Giaquinta[1], C. Funaioli[1], R. Berardi[3], C. Longobardi[1], E. Piana[1] & A. A. Martoni[1]

[1]Medical Oncology, S. Orsola-Malpighi Hospital, Bologna; [2]Medical Oncology, Falck Division, Niguarda Cà Granda Hospital, Milan; [3]Medical Oncology, University of Marche, Umberto I Hospital, Ancona; [4]Pathology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy

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Background: The purpose of this phase II study was to evaluate the efficacy and safety of cetuximab combined with FOLFIRI as a first-line treatment of advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Patients and methods: Untreated patients with confirmed advanced gastric or gastroesophageal adenocarcinoma received cetuximab at an initial dose of 400 mg/m^2 intravenously (i.v.) followed by weekly doses of 250 mg/m^2, CPT 11 180 mg/m^2 i.v. on day 1, LFA 100 mg/m^2 i.v. followed by 5-FU 400 mg/m^2 i.v. bolus, and 600 mg/m^2 i.v. 22-h continuous infusion on days 1 and 2 (FOLFIRI) every 2 weeks, for a maximum of 24 weeks, then cetuximab alone was allowed in patients with a complete response, partial response, or stable disease. Antitumor activity was assessed by computed tomography (CT) and positron emission tomography (PET) at baseline and after 6 weeks, and further by CT alone or CT and PET every 6 weeks.

Results: Thirty-eight patients were enrolled (median age 63.5 years, range 39–83; median Karnofsky performance status 90, range 70–100; stomach 89.5% and GEJ 10.5%; locally advanced disease 13.2% and metastatic disease 86.8%). All 38 patients were assessed for safety and survival, and 34 patients were assessed for overall response rates (ORR). The ORR was 44.1% [95% confidence interval (CI) 27.5% to 60.9%]. The median time-to-progression was 8 months (95% CI 7–9). At the median follow-up time of 11 months, 55.3% of patients were alive, with a median expected survival time of 16 months (95% CI 9–23). Grade 3–4 toxicity included neutropenia (42.1%), acne-like rash (21.1%), diarrhea (7.9%), asthenia (5.3%), stomatitis (5.3%), and hypertransaminasemia (5.3%). There was one (2.6%) treatment-related death.

Conclusions: The combination of cetuximab and FOLFIRI is active in gastric and GEJ adenocarcinoma. The higher toxicity appears to be limited to neutropenia.

Key words: advanced gastric cancer, Cetuximab, FOLFIRI regimen

introduction

Gastric cancer is the second leading cause of cancer death worldwide. It is expected that nearly 930 000 people per year will be diagnosed with gastric cancer, and that 700 000 will die of the disease [1]. In Italy, cancers of the stomach account for 7% of cancer deaths with 12 000 deaths per year [2]. Although the incidence of gastric cancer is declining in the Western world, adenocarcinomas of the gastroesophageal junction (GEJ) are increasing in number. There have been no major changes in the prognosis in the last 10–20 years.

In resectable cancer, surgery is potentially curative, but the majority of patients with gastric cancer have stage III or IV disease at presentation and so are candidates for chemotherapy. In advanced disease, the median survival in patients not receiving chemotherapy is 3–4 months. In a recent meta-analysis chemotherapy versus best supportive care and combination versus single agent, 5-fluorouracil (5-FU)-based chemotherapy mainly showed overall survival benefits in favor of chemotherapy and combination chemotherapy [3]. Although the current regimens yield overall response rates (ORR) of up to 51%, the median overall survival (OS) time in patients with advanced disease remains <10 months. Currently, 1-year survival rate is <50% in stage III A and B disease and <25% in stage IV [4].

Irinotecan is a semisynthetic analogue of camptothecin, which has promising activity in combination with 5-FU in gastrointestinal cancers [5, 6]. Irinotecan monotherapy is active in patients with gastric cancer with response rates in phase II trials

Correspondence to: Dr C. Pinto, Medical Oncology Unit, S. Orsola-Malpighi Hospital, Via Albertoni 15, 40138 Bologna, Italy; E-mail: cpinto@aosp.bo.it

of 14%–23% [7–11]. This drug is also active when administered with 5-FU/folinic acid, in phase II studies this combination yields ORR of 21%–40% and median OS times of 6.4–11.3 months [12, 13]. In large phase III study, irinotecan plus 5-FU regimen showed a trend of time to progression (TTP) that was superior as compared with cisplatin plus 5-FU (5.0 versus 4.2 months), similar ORR (31.8% versus 25.8%), and median OS time (9.0 versus 8.7 months), but a better safety profile [14].

The biweekly 5-FU/folinic acid (LV5FU2) regimen associated with irinotecan (FOLFIRI) is a manageable and active combination in metastatic colorectal cancer and it is largely used in Europe [5]. In a three-arm randomized phase II study for advanced gastric cancer, the FOLFIRI regimen compared with LV5FU2 or LV5FU2 plus cisplatin was not only more active but also well tolerated [12].

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is a member of the tyrosine kinase growth factor receptor superfamily. EGFR represents a promising new therapeutic target in cancer. EGFR is expressed in many normal human tissues and has been found overexpressed in a large variety of tumors [15]. In gastric cancer, EGFR is overexpressed in 18%–81% of primary tumor and/or metastasis [16–18].

Cetuximab (Erbitux, Merck KgaA, Darmstadt, Germany) is a human–murine chimeric monoclonal antibody (mAb) directed to the EGFR binding site. In a preclinical setting, cetuximab has demonstrated anticancer activity both in cell culture experiments and in the *in vivo* tumor xenograft animal model. In clinical experiences, cetuximab has shown an activity in a variety of tumors, including colorectal cancer [19–21]. Furthermore, clinical results have indicated that cetuximab may overcome resistance to irinotecan [22–24]. Although cetuximab has a modest activity as monotherapy in some systems, it has consistently demonstrated a better activity when administered in combination with cytotoxic chemotherapy. The efficacy of cetuximab was further confirmed by a randomized phase II trial in which cetuximab alone was compared with a combination of cetuximab and irinotecan in EGFR-positive advanced colorectal cancer patients who progressed to an irinotecan-based chemotherapy regimen. ORR was 10.8% for cetuximab alone and 22.9% for cetuximab plus irinotecan [25].

Given these data, this phase II study was carried out to evaluate the efficacy and toxicity of a regimen combining a targeted therapy, cetuximab, with an established 5-FU, *levo*-folinic acid and irinotecan (FOLFIRI regimen) chemotherapy, for unresectable locally advanced or metastatic gastric and GEJ adenocarcinoma.

patients and methods

study design

We conducted a multicenter phase II study that was approved by the local ethical committee, registered with the health authorities, and carried out according to the guidelines of good clinical practice and the Declaration of Helsinki. The primary end point was objective response. Secondary end points were toxicity, median survival, and TtP.

patient eligibility

Patients with advanced, unresectable, histologically confirmed adenocarcinoma of the stomach or GEJ were assessed for eligibility. Eligibility criteria were age ≥18 years, Karnofsky performance status (KPS) ≥70, life expectancy ≥3 months, no previous treatment with chemotherapy or radiation therapy, neutrophil count ≥1500/μl, platelet count ≥100.000/μl, hemoglobin ≥9.0 g/dl, serum creatinine ≤1.5 × upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN (≤5 × ULN in the presence of liver metastases), total bilirubin ≤1.5 × ULN, EGFR expression in primary, and/or metastatic tumor demonstrated by immunohistochemistry, measurable disease according to the response evaluation criteria in solid tumors (RECIST) [26]. Prior chemotherapy for advanced cancer was not allowed. Patients who received adjuvant therapy were eligible provided >6 months had relapsed between the end of adjuvant therapy and registration on the study. All the patients provided written informed consent for this study, which was approved by the ethics committee of each participating institution. Patients were considered ineligible for the trial if they satisfied any of the following criteria: previous exposure to anti-EGFR mAbs, signal transduction inhibitors, or EGFR-targeting therapy; brain metastasis; concurrent malignancy other than nonmelanoma skin cancer, or *in situ* cervix carcinoma (patients with a previous malignancy but with no evidence of disease for ≥5 years were allowed to enter the trial); clinically relevant coronary artery disease or history of a myocardial infarction within the last 12 months; acute or subacute intestinal occlusion or history of the inflammatory bowel disease; known grade 3 or 4 allergic reaction to any of the components of the treatment; pregnancy or lactating status; and medical or psychological condition which, in the opinion of the investigator, would not enable the patient to complete the study or knowingly sign the informed consent.

EGFR expression

The EGFR assessment on primary tumor and/or metastasis was carried out centrally at the S. Orsola-Malpighi Hospital of Bologna to avoid any discrepant evaluation. The assessment was carried out using the EGFR PharmDx kit System (DakoCytomation). EGFR immunostained cells were quantitatively evaluated and scored as follows: score 0 if <1%; score 1 if >1% and <20%; score 2 if >20% and <50%; score 3 if >50% and <80%; and score 4 if >80% of neoplastic cells immunopositive. Staining intensity was also recorded using a categorical classification: score 1 (weak), score 2 (moderate), and score 3 (strong) immunostaining. Where the neoplastic population shows a patchy, nonuniform staining intensity the value is referred to the prevalent immunostained intensity. A final score is obtained combining the two score values (sum) ranging from 0 to 7, and categorized into: low (0–2), intermediate (3–5), and high (6–7). The EGFR expression was scored by only one pathologist.

pretreatment evaluations

The baseline evaluation included history, physical examination (including evaluation of vital signs and performance status), recording of concomitant medication, laboratory tests (hematology and clinical chemistry, carcinoembryonic antigen, CA 19.9, CA 72.4), thorax and abdomen computed tomography or magnetic resonance imaging, and positron emission tomography (PET) scan.

treatment

Patients received cetuximab at an initial dose of 400 mg/m^2 i.v. followed by weekly doses of 250 mg/m^2, irinotecan (Campto, Pfizer) 180 mg/m^2 i.v. on day 1, *levo*-folinic acid 100 mg/m^2 i.v. followed by 5-FU 400 mg/m^2 i.v. bolus and 600 mg/m^2 i.v. 22-h continuous infusion on days 1 and 2 (FOLFIRI regimen) every 2 weeks, for a maximum of 24 weeks, then cetuximab alone was allowed in patients with complete response, partial response, and stable disease (maintenance therapy). Patients benefiting from combination therapy but developing unacceptable intolerance/toxicity to cetuximab or FOLFIRI, FOLFIRI or cetuximab may be continued as a single treatment,

and vice versa. Surgery of locally advanced gastric cancer could be carried out during the study at the time of the maximum of the regression under previous assessment of tumor response after at least 12 weeks of treatment (at least two response assessments). If a complete resection was achieved, patients would restart the treatment up to a maximum of 24 weeks (adding pre and postsurgery treatment).

dose modifications

If a patient experiences grade 3 skin toxicity, cetuximab therapy may be deferred for up to two consecutive infusions without changing the dose level. If the toxicity resolves to grade 2 or less by the following treatment period, the treatment may resume. With the second and third occurrences of a grade 3 skin toxicity, cetuximab therapy may again be deferred for up to two consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively. Patients should discontinue cetuximab if more than two consecutive infusions are withheld or a fourth occurrence of a grade 3 skin toxicity occurs despite an appropriate dose reduction. Chemotherapy was continued independently of temporary interruption of cetuximab. Cetuximab was not withheld for FOLFIRI-related toxicity. FOLFIRI dose reduction was planned in the event of severe hematological and/or non-hematological toxic effects. In cases of insufficient hematological function (neutrophil count <1500/μl and platelet count <100.000/μl) chemotherapy was delayed for up to 14 days. If no recovery occurred at this point, the treatment was discontinued. For grade 3–4 gastrointestinal toxic effects, thrombocytopenia, and neutropenia there were 20% irinotecan and 5-FU dose reductions.

evaluation during therapy

Routine evaluation of patients was carried out on a weekly basis during therapy. These evaluations included a physical examination, vital signs, KPS, laboratory hematological and serum chemistry, and the recording of adverse events.

efficacy and toxicity assessment

The response evaluation of the tumor to therapy was based on computed tomography or magnetic resonance scan. Patients are assessable for response if they have received at least one course of therapy. In addition, those patients developing rapid tumor progression, or who die of progressive disease, before response evaluation, will also be considered assessable for response. Also patients who discontinue treatment, or who die, due to a treatment-related toxicity before response evaluation are considered assessable for response. The tumor was evaluated every 6 weeks during the treatment and at least every 12 weeks during the follow-up. RECIST were used to assess the type of response [26]. A complete response was defined as the complete disappearance of all target tumor lesions. A partial response was defined as a 30% decrease at least in the sum of the longest diameter (LD) of target lesions taking as reference the smallest sum LD. Tumor progressive disease was defined as a 20% increase at least in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease taking as references the smallest sum LD. PET scan was carried out every 6 weeks during the treatment. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria Version 3.0 [27].

statistical considerations

Statistical design was carried out according to the Gehan's two-stage phase II optimal trial design [28]. It is assumed that the likelihood of response to treatment is $\pi = 0.3$ (0.20−0.40). The number of patients to be recruited to the first stage of the phase II trial is n_1, while r1 are responses observed in these n_1 patients. If r1 > 0 then n_2 patients are recruited to the second stage, giving a total of $N = n_1 + n_2$ patients in all. The value of n_2 is chosen to give a specified precision ε, for the final estimate of the efficacy π. The probability of rejecting the treatment combination with an efficacy at least 20% is <0.05. This means that $\pi = 0.20$, $1-\beta = 0.95$, $\varepsilon = 0.10$. Initially $n_1 = 14$ patients had to be enrolled in the first stage. If none of the $n_1 = 14$ patients showed an objective response, the trial could be terminated. If at least one response was observed in the first group of 14 patients, the study could proceed to the second stage. Considering an expected response of 40%, the number of patients should be recruited in the second stage is $n_2 = 11$ that gives a total number of $N = n_1 + n_2 = 25$ patients. Finally, a total number of 38 patients were enrolled. TTP and OS were calculated using the Kaplan–Meier method [29]. Descriptive statistics were used for safety evaluation. A 40% ORR was considered sufficiently assessable to pursue this combination in a phase III trial.

results

patients population

From November 2004 to December 2005, 49 out of 54 (90.7%) screened subjects were EGFR positive, and 38 patients were enrolled in the study. Eleven EGFR-positive patients were excluded for the worsening of their performance status (six patients), treatment refusal (four patients), and myocardial infarction before the recruitment (one patient). All 38 enrolled patients were evaluated for safety and OS calculations and 34 were assessable for response. Four patients were not assessable for ORR because one patient died as a result of a disseminated intravascular coagulation in week two of treatment (baseline platelet count <139.000/μl; no prophylactic heparin during treatment); one died of myocardial infarction after required intervention for displacement in central venous access device in week two; one died of gastric bleeding during esophagogastroscopy in week four after achieving an objective and subjective improvement; and there was one treatment-related death for febrile neutropenia before the second week of therapy. Among the four patients who were not assessable for ORR, three received just 2 weeks of treatment and one (who clinically improved) 4 weeks.

The patient characteristics are listed in Table 1. The majority of patients were males (68.4%), their median age being 63.5 years (range 39–83) and the median KPS 90 (range 70–100). GEJ was involved in four patients (10.5%). The histotype was intestinal adenocarcinoma in 25 patients (65.8%) and nonintestinal adenocarcinoma in 13 (34.2%). At the baseline of the study, five patients (13.2%) had unresectable locally advanced disease and 33 (86.8%) metastatic disease. The majority of patients (76.3%) had two or more metastases sites. Fourteen patients (36.8%) had received prior adjuvant chemotherapy.

treatment administration

In total, 704 weeks of treatment were administered, with a median of 13 weeks (range 1–55). The median relative dose intensity was 0.90 for cetuximab (range 0.80–1.0), 0.90 for irinotecan (range 0.20–1.0), and 0.90 for 5-FU (range 0.20–1.0) (Table 2).

Cetuximab was discontinued in two patients after 9 and 20 weeks of treatment of grade 4 cutaneous toxicity; no cetuximab

Table 1. Patient characteristics

Characteristics	No. 38	
	No. of patients	%
Sex		
Male	26	68.4
Female	12	31.6
Age, years		
Median	63.5	
Range	39–83	
Karnofsky performance status		
100	6	15.8
90	16	42.1
80	9	23.7
70	7	18.4
Primary tumor site		
Stomach	34	89.5
Gastroesophageal junction	4	10.5
Histology		
Intestinal adenocarcinoma	25	65.8
Nonintestinal adenocarcinoma	13	34.2
Disease status		
Locally advanced	5	13.2
Metastatic	33	86.8
Prior surgery	23	60.5
Curative	19	50
Adjuvant chemotherapy	14	36.8
5-FU/CDDP regimens	5	13.2
5-FU/CDDP/EPI regimens	5	13.2
Others regimens	4	10.5
No. of organs involved		
1	9	23.7
2	24	63.2
>2	5	13.1
Sites of disease		
Lymph nodes	20	52.6
Peritoneum/recurrence	15	39.5
Liver	12	31.6
Lung	4	10.5

reduction dose was carried out. At least a one dose reduction of 5-FU and irinotecan (FOLFIRI regimen) in 19 patients (50.0%) was required. Neutropenia was the most frequent reason for the high rate of the FOLFIRI dose reduction.

Maintenance therapy (after 24 weeks of cetuximab plus FOLFIRI treatment) was carried out in 12 patients (31.6%). The median duration of maintenance treatment was 10 weeks (range 3–31).

response

The data on treatment response are listed in Table 3. Four patients (11.8%) achieved a complete response and 11 patients (32.4%) a partial response; the ORR was 44.1% (95% CI 27.5% to 60.9%). Sixteen patients (47.1%) had stable disease and three patients (8.8%) progressive disease. The disease control (complete response plus partial response plus stable disease) was 91.2%. The median time-to-response was 6 weeks (range 6–18).

Table 2. Summary of study drug administration

Weeks of treatment given	704		
Median	13		
Range	1–55		
	Cetuximab	Irinotecan	5-fluorouracil
Median relative dose intensity	0.90	0.90	0.90
Range	0.8–1.0	0.2–1.0	0.2–1.0

Table 3. Efficacy data

	No. 34	
	No. of patients	%
Complete response	4	11.8
Partial response	11	32.4
Overall response rate (95% CI)	15	44.1 (27.5% to 60.9%)
Stable disease	16	47.1
Progressive disease	3	8.8
Time to progression, months (95% CI)	8 (7–9)	

CI, confidence interval.

The objective response was similar in both histotypes (intestinal and nonintestinal adenocarcinoma) (Table 4). The degree of EGFR expression, either as the percentage of EGFR-positive tumor cells or the staining intensity per cell according to German score [30] did not correlate with the ORR (Table 5). The ORR in patients with grade <2 skin reactions after cetuximab therapy were higher, but not significantly, than those in patients with ≥2 grade (Table 5). The adjuvant chemotherapy did not affect the treatment response. The objective responses in the 14 patients previously treated with adjuvant therapy were three complete responses, three partial responses, and eight stable diseases.

One patient with unresectable locally advanced disease achieved a partial response after 13 weeks of treatment and was submitted to total gastrectomy R0 (patient evaluated as partial response in the ORR). Among the other four patients with unresectable locally advanced disease one was not assessable for response, one achieved a partial response (the response did not permit surgery), and two obtained a stable disease.

Eleven (32.4%) patients received a second-line treatment; five cisplatin plus epirubicin, two cisplatin plus 5-FU continuous infusion, one cisplatin plus epirubicin plus 5-FU continuous infusion, one carboplatin plus 5-FU continuous infusion, one 5-FU plus *levo*-folinic acid plus oxaliplatin (FOLFOX4), and one docetaxel (Taxotere, Sanofi Aventis).

TTP and survival

The median TTP, assessed in 34 patients, was 8 months (95% CI 7–9) (Figure 1). At the median follow-up time of 11 months (range 5–20), 21 of 38 patients (55.3%) were alive. At this time the median OS had not yet been reached. The median OS

Table 4. Objective responses according to histotype

	Intestinal adenocarcinoma (No. 22)		Nonintestinal adenocarcinoma (No.12)		Total (No. 34)	
	No. of patients	%	No. of patients	%	No. of patients	%
Complete response	3	13.6	1	8.3	4	11.8
Partial response	7	31.8	4	33.3	11	32.3
Overall response rate (95% confidence interval)	10	45.4 (24.6% to 66.2%)	5	41.6 (13.7% to 69.5%)	15	44.1 (27.5% to 60.9%)
Stable disease	9	40.9	7	58.3	16	47.1
Progressive disease	3	13.6	0	–	3	8.8

Table 5. Influence of EGFR expression and rash on response rates

	Complete response + partial response		*P* value for trend
	No. of patients	%	
EGFR (German score)[a]			0.20
EGFR negative	7/17	41.2	
EGFR intermediate	5/9	55.6	
EGFR positive	3/6	50	
Total	15/32	46.8	
Acne-like rash			0.68
Grade <2	5/15	33.3	
Grade ≥2	10/19	52.6	

[a]Two patients were not assessable.

EGFR, epidermal growth factor receptor.

time estimated in all 38 patients is 16 months (95% CI 9–23) (Figure 2).

safety

All 38 patients were evaluated for toxicity (Table 6). The major toxicity observed was hematological. Grade 3–4 neutropenia occurred in 16 patients (42.1%). Febrile neutropenia occurred in two patients (5.3%) and one of them died of febrile neutropenia after the first week's therapy.

Non-hematological toxic effects were generally mild in severity. The most common grade 3–4 non-hematological toxic effects were diarrhea (7.9%), asthenia (5.3%), stomatitis (5.3%), hypertransaminasemia (5.3%), and vomiting (2.6%).

No cetuximab-related hypersensivity reaction was reported. Acne-like rash occurred in 31 patients (81.6%), but grade 3 and 4 skin toxicity was observed in only six (15.8%) and two (5.3%) patients, respectively. Cetuximab was discontinued in two patients with grade 4 cutaneous toxicity after 9 and 20 weeks. Grade 1 or 2 of hypomagnesemia was recorded in 13 (34.2%) patients; grade 3 or 4 of hypomagnesemia was not observed.

discussion

Unresectable advanced or metastatic gastric cancer still has a poor prognosis, with a median survival of just 7–10 months. Several combinations regimens of chemotherapy have been developed, but the survival advantage appears to be marginal,

Figure 1. Kaplan–Meier plot for time-to-progression.

and no worldwide standard regimens have as yet been established. Recent meta-analysis has been carried out to assess the efficacy and tolerability of chemotherapy in patients with advanced gastric cancer. Analysis of chemotherapy versus best supportive care (Hazard Ratio/HR = 0.39, CI 95% 0.28–0.52) and combination versus single agent, mainly 5-FU, (HR = 0.83, 95% CI 0.74–0.93) demonstrated significant OS results in favor of chemotherapy and combination chemotherapy. Furthermore, comparisons of 5-FU/cisplatin-containing regimens with versus without anthracyclines (HR = 0.77, 95% CI 0.62–0.95) and 5-FU/anthracycline-containing combinations with versus without cisplatin (HR = 0.83, 95% CI 0.76–0.91) both showed a significant survival benefit for the three-drug combination. In addition, comparison of irinotecan-containing versus nonirinotecan-containing combinations demonstrated a nonsignificant survival benefit in favor of the irinotecan-containing regimens (HR = 0.88, 95% CI 0.73–1.06), but they have never been compared with three-drug regimens containing 5-FU/cisplatin and anthrayclines [3].

Three recently published randomized trials included chemotherapy combinations of infusional 5-FU and irinotecan. In FFCD 9803 randomized phase II study, 134 patients with untreated metastatic gastric cancer received biweekly regimen of

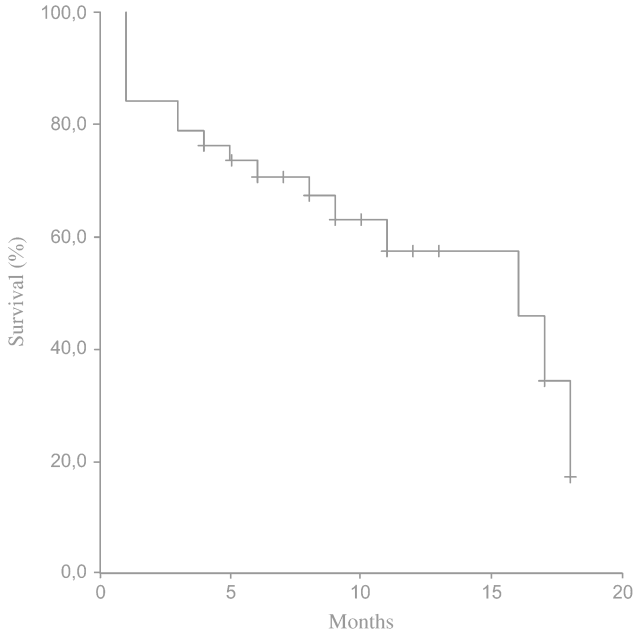

Figure 2. Kaplan–Meier plot for overall survival.

Table 6. Hematological and non-hematological toxicity

Toxicity	No. 38			
	All grades		Grade 3–4	
	No. of patients	%	No. of patients	%
Hematological toxicity				
Neutropenia[a]	19	50	16	42.1
Anemia	26	68.5	1	2.6
Thrombocytopenia	1	2.6	1	2.6
Non-hematological toxicity				
Acne-like rash	31	81.6	8	21.1
Diarrhea	19	50.0	3	7.9
Asthenia	28	73.7	2	5.3
Stomatitis	14	36.8	2	5.3
Hypertransaminasemia	10	26.3	2	5.3
Hyperbilirubinemia	7	18.4	1	2.6
Vomiting	9	23.7	1	2.6
Anorexia	16	42.1	0	–
Hypomagnesemia	13	34.2	0	–
Nausea	12	31.6	0	–
Alopecia	12	31.6	0	–

[a]One patient died for febrile neutropenia.

5-FU and leucovorin (LV5FU2), or LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan (FOLFIRI). The ORR were 13%, 27%, and 40% for LV5FU2, LV5FU2-cisplatin, and FOLFIRI, respectively. Median TTP and OS times were 3.2 months and 6.8 months with LV5FU2; 4.9 months and 9.5 months with LV5FU2-cisplatin; and 6.9 months and 11.3 months with FOLFIRI [12]. In a phase II study, 114 untreated patients with metastatic gastric adenocarcinoma were randomized to receive either 5-FU and leucovorin plus etoposide (ELF) or irinotecan plus high-dose 5-FU and leucovorin (ILF). ORR for ILF and ELF were 43% and 24%, respectively. For ILF and ELF, respectively, median TTP was 4.5 versus 2.3 months and OS was 10.8 versus 8.3 months [13]. In large phase III trial, 333 patients were randomized to receive irinotecan plus high-dose 5-FU and leucovorin (IF) or cisplatin and 5-FU (CF). The IF regime did not demonstrated superiority versus CF for TTP 5.0 versus 4.2 months, median OS time 9.0 versus 8.7 months, and ORR 31.8% versus 25.8%, respectively, but showed a better safety profile [14]. According to meta-analysis, irinotecan regimens show a benefit in survival of ~1 month and a lower rate of treatment-related deaths over the reference regimen [3].

Recently developed new agents, such camptothecins, taxanes, platinum analogue, and oral fluopyrimidines, have been investigated in clinical trials. Contrary to the recent advances in colorectal cancer, no confirmation of improved results with newer-generation regimens as compared with older-generation ones has yet been achieved.

Molecular targeting agents are another new topic in the field of cancer therapy, and may provide a significant impact also in gastric cancer treatment, as successful results have observed in colorectal cancer [25]. Epidermal growth factor (EGF) is a polypeptide that, through its receptor (EGFR), stimulates the proliferation and differentiation of both normal and malignant cells [31]. EGF has been shown immunohistochemically to be present in 25%–30% of gastric cancers (EGF-positive area). The presence of EGF in gastric cancer is correlated with the degree of gastric wall invasion and lymph nodes metastasis. The 5-year survival of patients with EGF-positive tumors is worse than that of patients with EGF-negative tumors. The presence of EGF in human gastric cancer may therefore represent a higher malignant potential. There have been numerous studies examining the EGFR overexpression in gastric cancer; however, the reported frequencies vary widely, ranging from 18% to 81%. An increase of EGFR protein expression in gastric cancer appears to be related to biological aggressiveness, although gene amplification has occurred only to a small extent. Tumors exhibiting EGF and EGFR simultaneously show a greater degree of local invasion and lymph node metastasis [16–18].

In several phase I and II studies, tyrosine kinase inhibitors and a mAb directed to the EGFR have been evaluated in patients with gastric and GEJ adenocarcinoma. Gefitinib (Iressa, Astra-Zeneca) was administered at 250 or 500 mg daily in 75 patients (32 of whom Japanese) with advanced gastric cancer that had progressed to one or two previous chemotherapy regimens. Clinical activity was modest, with only 1% of patients achieving a partial response and 16% presenting a stable disease [32]. In a second study, 20 pretreated patients with esophageal or GEJ carcinoma (12 patients with GEJ and seven with distal esophageal adenocarcinoma; and one with a proximal esophageal squamous cell carcinoma) received gefitinib at 250 mg daily. The 15% of the patients achieved a partial response and 15% a stable disease [33]. Erlotinib (Tarceva, Roche) was evaluated in 70 untreated patients with either gastric (25 patients) or GEJ (45 patients) adenocarcinoma at the dose of 150 mg daily. None of the patients in the gastric cancer cohort presented an objective response and an ORR of 12% was observed in the GEJ group [34]. To sum up, the tyrosine kinase

inhibitors, gefitinib and erlotinib, seem to be ineffective in patients with advanced gastric cancer. In a phase I study, humanized anti-EGFR antibody matuzumab (EMD 72000) was evaluated in combination with epirubicin, cisplatin, and capecitabine (ECX) as a first-line treatment of advanced gastric, GEJ, or lower esophagus adenocarcinoma. The best overall response (partial response plus stable disease) in 17 treated patients at 400 and 800 mg dose of matuzumab, was 57% and 43%, respectively. Matuzumab in association with the ECX regimen appears to be tolerated, and preliminary efficacy data indicate antitumor activity [35].

In the FOLCETUX trial, the primary end point was ORR. ORR of 44.1% in 34 assessable patients is encouraging, especially in view of the tolerance of this combination. The major toxicity appears to be limited to neutropenia (42.1% of grade 3–4). The typical side effects associated with cetuximab are skin reactions (21.1% of grade 3–4), whereas the other side effects were moderate and not aggravated by cetuximab. Severe diarrhea was observed in 7.9% of patients and it was mainly grade 3. There was one (2.6%) treatment-related death from febrile neutropenia.

Treatment achieved the same ORR in both different histotypes, intestinal and nonintestinal adenocarcinoma. Subgroup analysis also showed that there does not seem to be a correlation between the EGFR expression level in the target tumor and the treatment activity. This is similar to the results of another study using cetuximab in combination with irinotecan to treat patients with metastatic colorectal cancer [25]. We observed a link (not statistically significant) between treatment activity and the severity of cetuximab-induced skin reactions, as reported in the other study with cetuximab-based therapy [25].

In the two phase II and the phase III randomized trials, the infusional 5-FU and irinotecan combination arms showed a median OS times of 10.8, 11.3 and 9.0 months [12–14]. In the FOLCETUX study, the addition of cetuximab to FOLFIRI regimen produced an estimated median survival of 16 months, with 55.3% of patients still alive at the median follow-up time of 11 months.

Tolerance of treatment and quality of life are of considerable importance in patients with advanced gastric cancer because a majority of patients have symptoms at baseline. In this context, cetuximab and FOLFIRI combination therapy resulted in a longer TTP and OS but also in an acceptable level of safety and a shorter time-to-response (6 weeks), and therefore this can have an impact on the quality of life. A treatment with a median TTP of 8 months and a median OS time of 16 months may indicate an improvement in the treatment of advanced gastric cancer.

In conclusion, we found that the combination of cetuximab and *levo*-folinic acid, 5-FU, and irinotecan (FOLFIRI regimen) is active with an acceptable rate of toxicity in the first-line treatment of advanced gastric or GEJ adenocarcinoma. In order to increase the survival of patients with gastric cancer, future studies should investigate new strategies with novel drugs (e.g. camptothecins, taxanes, platinum analogue, and oral fluopyrimidines) in combination with cetuximab under different settings, including neo-adjuvant, adjuvant, and palliative chemotherapy.

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