Journal of Cell Science & Therapy

Azmy et al., J Cell Sci Ther 2012, 3:4
DOI: 10.4172/2157-7013.1000125

Research Article Open Access

Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared with Infusional Fluorouracil, Levcovorin, and Irinotecan (FOLFIRI) as First-Line Treatment for Metastatic Colorectal Cancer

Aly M. Azmy, Khalid Elhusseiny Nasr, Nagy Samy Gobran* and Mohamed Yassin Mostafa

Department of Medicine, Ain Shams University, Cairo, Egypt

Abstract

Rationale: This phase III study was conducted to compare fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first line management of metastatic colorectal carcinoma.

Methods: Sixty patients with unresectable metastatic colorectal adenocarcinoma were randomly assigned to FOLFOXIRI (n = 30) or FOLFIRI (n = 30) as first line for metastatic disease. The primary end point was response rate (RR) and secondary end points were progression free survival (PFS), overall survival (OS), post chemotherapy RO surgical resection (complete resection with safety margin), and toxicity.

Results: The RR was significantly higher for FOLFOXIRI arm 60% (18/30) compared to FOLFIRI (33%) (p = 0.007). The rate of progression was significantly lower for patients treated with FOLFOXIRI (11% vs. 24%; p = 0.02), 5 patients (16%) underwent radical (RO) surgery of metastases in the FOLFOXIRI arm compared with one patient (3%) in the FOLFIRI arm (p = 0.02). FOLFOXIRI resulted in an increased PFS, with median PFS of 10 month vs. 7.5 months (p = 0.0099) with an HR for progression of 2.58 (95% CI, 1.2 to 5.3). The rate of early progression (patients who progressed within six months from the treatment onset) was significantly lower in the FOLFOXIRI arm (18% vs. 45%; p < 0.0001); OS is significantly longer for FOLFOXIRI (22.6 vs. 16.7 months; p = 0.032) corresponding to an HR for death of 0.70 (95% CI, 0.50 to 0.96). Patients who received FOLFOXIRI were subjected to significantly higher incidence of adverse events; grade 2 to 3 peripheral neurotoxicity (0% vs. 20%; p < 0.001) and grade 3 to 4 neutropenia (26% vs. 53%; p < 0.001). Febrile neutropenia was comparable between the two arms (3% vs. 6%) of patients; p = 2.

Conclusion: Compared to FOLFIRI regimen; FOLFOXIRI regimen has significantly higher RR, PFS, OS, and improved chance for resection of metastases, with higher but tolerable toxicity in patients with metastatic colorectal cancer.

Keywords: Metastatic colorectal carcinoma; FOLFOXIRI; FOLFIRI

Introduction

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2011, there was an estimated 101340 new cases of colon cancer and approximately 39870 cases of rectal cancer. During the same year it was estimated that 49380 people will die from colon and rectal cancer combined [1].

Despite these statistics, the incidence per 100000 populations of colon and rectal cancers has decreased from 60.5 in 1976 to 46.4 in 2005 [2].

In addition, mortality from colorectal cancer has decreased by almost 35% from 1990 to 2007 [1] possibly because of earlier diagnosis through screening and better treatment modalities.

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop metastases [3-5], and 80-90% of these have unresectable metastatic liver disease [4,6-8]. Use of FOLFOXIRI compared with FOLFIRI as initial therapy for treatment of metastatic disease has been investigated in 2 randomized phase III trials [9,10]. In one study statistically significant improvements in (PFS) progression free survival (9.8 months vs. 6.9 months; hazard ratio = 0.63; p = 0.0006) and median overall survival (OS) (22.6 months vs. 16.7 months; hazard ratio = 0.70; p = 0.032) were observed in the FOLFOXIRI arm [9], although there was no overall survival difference between the 2 treatment arms in the other study (median overall survival 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; p = 0.0337) [10].

Both studies showed some increased toxicities in the FOLFOXIRI arm (e.g. significant increase in neurotoxicity and neutropenia [9], diarrhea, alopecia and neurotoxicity [10] but no difference in the rate of toxic death were reported in either study.

Patients and Methods

This trial was conducted at Ain Shams University hospital from Nov

***Corresponding author:** Nagy Samy Gobran, Department of Medicine, Ain Shams University, Cairo, Egypt, E-mail: nagy_gobran@yahoo.com

Received March 13, 2012; **Accepted** May 09, 2012; **Published** May 11, 2012

Citation: Azmy AM, Nasr KE, Gobran NS, Mostafa MY (2012) Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared with Infusional Fluorouracil, Levcovorin, and Irinotecan (FOLFIRI) as First-Line Treatment for Metastatic Colorectal Cancer. J Cell Sci Ther 3:125. doi:10.4172/2157-7013.1000125

2008 to Jan 2011 with the following eligibility criteria: adenocarcinoma of the colon or rectum, unresectable metastatic disease, age 18 to 70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower, measurable disease according to WHO criteria, leukocyte count of at least 3.500/mm^3, neutrophils count of at least 1.500/mm, platelet count of at least 100.000/mm^3, serum Creatinine of 1.3 mg/dL or less, serum bilirubin less than 1.5 mg/dL and AST, ALT and alkaline phsophatase 2.5x normal values or less (≤ 5 if liver metastases).

Exclusion criteria were previous palliative chemotherapy for metastatic disease, previous chemotherapy including irinotecan or oxaliplatin, neuropathy ≥ grade 2, symptomatic cardiac disease, myocardial infarction in the last 24 months or uncontrolled arrhythmia, active infection, inflammatory bowel disease, and total colectomy. Previous fluoropyrimidine based adjuvant chemotherapy was allowed if ended more than 6 months before random assignment.

Sixty eligible patients were enrolled onto the study, stratified according to ECOG performance status (0, 1, or 2), then randomly assigned to FOLFIRI (arm A) (n = 30) or FOLFOXIRI (arm B) (n = 30) after signing a written consent. Treatment was administered every 2 weeks until evidence of progression, unacceptable toxicity, patient refusal, after 2 months of maximum response, or for a maximum of 12 cycles. Patients in arm A received FOLFIRI protocol in the following schedule: premedication with ondansetron 8 mg, dexamethasone 8 mg, ranitidine IV (intravenous), CPT-11 (irinotecan) 180 mg/m^2 IV infusion over one hour day 1, leucovorin 100 mg/m^2 IV infusion over 2 hours day 1, and 2, 5-FU 400 mg/m^2 IV bolus injection day 1, and 2, 5-FU 600 mg/m^2 IV infusion over 22 hours day 1, and 2. patients in arm B were subjected to FOLFOXIRI protocol in the following schedule: lrinotecan 180 mg/m^2 day 1 IV infusion over one hour, oxaliplatin 85 mg/m^2 day 1 over 2 hours, leucovorin 200 mg/m^2 day 1 over 2 hours, fluorouracil 3200 mg/m^2 day 1 48-hour continuous infusion starting on day 1, every 2 weeks. Complete blood count, liver function tests, kidney function tests, reporting of adverse effects were done before each cycle in both arms.

Adverse events were evaluated according to National Cancer Institute common toxicity criteria version 4.0 Responses were evaluated every 8 weeks according to WHO criteria. Grade 3 and 4 toxicities were managed symptomatically, and with G-CSF (Granulocyte- Colony Stimulating Factor), and blood transfusion in case of hematological toxicity, with subsequent 25% dose reduction of the frequent cycles. The following chemotherapy cycle was postponed till recovery. In cases of grade 3 and 4 diarrhea, dose reduction was done only for CPT-11, and 5-FU.

The primary study end point was response rate (RR). Secondary end points were PFS, OS and post-chemotherapy RO surgical resections (complete surgical resection with adequate margin), and toxicity. Response assessment was done by computed tomography after 2 months from the start of therapy, and every 2 months thereafter. Response was assessed according to the WHO criteria. PFS was defined as the length of time from random assignment to disease progression or to death resulting from any cause whichever occurred first or to last contact. The evaluation of PFS was based on investigators assessment. OS was defined as the length of time from random assignment to death or to last contact. We tested the 14 following variables as possible predictive factors for objective response or surgical RO resection and as possible prognostic factors: treatment, sex, age (< or ≥ 65 years), WHO performance status (0 or 1 to 2), primary tumor site (colon or rectum), number of organs involved (single or multiple), sites of disease (liver only or other sites), liver involvement (< or ≥ 25%), time from first diagnosis to first metastases (0 to 3 , 3 to 12 , or > 12 months), previous adjuvant therapy (yes or no), baseline lactate dehydrogenase (normal or ≥ upper limit of normal), baseline carcinoembryonic antigen (< or ≥ 100ng/mL), baseline leukocyte (< or ≥ 8.000/mL), and baseline hemoglobin (< or ≥10g/dL). Patients' characteristics are shown in Table 1.

Statistical analysis

The required number of patients for this study was determined according to a Simon optimal design for a goal of 10% success at maximal model; an accrual of 30 patients assessable for response for each arm was planned. All multivariate analyses used a step-down procedure based on the likelihood ratio test. Multivariate analyses were done on the intention to treat population. A logistic regression model was used to identify the predictive factors for objective response and surgical RO resection. For time to progression and OS, Cox's proportional hazards modeling were used. Statistical analysis was performed using Graph pad prism statistical software version 5.01.

Results

All randomly assigned patients received at least one cycle of study treatment and were evaluated for safety. Both treatments were relatively well tolerated and associated with manageable toxicities. The median number of administered cycles was 9 in the FOLFIRI arm and 8 in the FOLFOXIRI arm; the relative dose-intensity of administered FU, CPT-11 and Oxaliplatin ranged between 82% and 87% of planned for all agents in both arms. Treatment interruption because of toxicity were 10% for FOLFIRI and 13% for FOLFOXIRI (p = 0.08). No toxic death occurred. Most commonly observed toxicities were neutropenia, diarrhea, nausea and vomiting, sensory neurotoxicity, stomatitis, alopecia, and thrombocytopenia (Table 2). Grade 3 to 4 toxicities, were

Characteristic	FOLFIRI		FOLFOXIRI	
	No.	%	No.	%
Sex				
Male	17	57	15	50
Female	13	43	15	50
ECOG performance status				
0	5	17	4	13
1	20	66	21	70
2	5	17	5	17
Age, years				
Median	51		53	
Range	22-69		26-66	
Previous adjuvant chemotherapy				
Yes	29	97	28	94
No	1	3	2	6
No. of involved organs				
1	29	97	27	91
> 1	1	3	3	9
Liver only metastases				
Yes	29	97	27	91
No	1	3	3	9
CEA				
< 100	15	50	11	36
≥ 100	15	50	19	64
Liver metastases				
< 25%	17	59	17	63
≥ 25%	12	41	10	37

Table 1: Patient characteristics.

Citation: Azmy AM, Nasr KE, Gobran NS, Mostafa MY (2012) Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared with Infusional Fluorouracil, Levcovorin, and Irinotecan (FOLFIRI) as First-Line Treatment for Metastatic Colorectal Cancer. J Cell Sci Ther 3:125. doi:10.4172/2157-7013.1000125

Characteristic	FOLFIRI		FOLFOXIRI		P (Grade $_{3/4}$)
	No.	%	No.	%	
Nausea Grade $_{1/2}$ Grade $_{3/4}$	24 1	80 3.33	28 2	93.3 6.7	NS
Vomiting Grade $_{1/2}$ Grade $_{3/4}$	16 1	53.33 3.33	20 2	66.66 6.66	NS
Diarrhea Grade $_{1/2}$ Grade ¾	13 6	43.33 20	16 9	53.2 30	NS
Stomatitis Grade $_{1/2}$ Grade ¾	16 2	53.33 6.66	24 4	80 13.33	NS
Neurotoxicity Grade $_{1/2}$ Grade ¾	0 0	0 0	18 6	60 20	< 0.0001
Toxicity (NCI-CTC grade)					
Asthenia Grade $_{1/2}$ Grade ¾	16 2	53.33 6.66	25 3	83.33 10	NS
Thrombocytopenia Grade $_{1/2}$ Grade ¾	6 1	20 3.33	14 2	46.66 6.66	NS
Anemia Grade $_{1/2}$ Grade ¾	16 1	53.33 3.33	26 3	86.66 10	NS
Neutropenia Grade $_{1/2}$ Grade ¾	11 8	36.66 26.66	14 16	46.66 53.4	0.0006
Febrile Neutropenia	1	3.33	2	6.66	NS

Table 2: Toxicity profile of the patients in both arms.

Response	FOLFIRI (n = 30)	FOLFOXIRI (n = 30)
Investigators assessment Complete Partial **Complete + Partial** 95% CI Stable disease Progression Not assessable	1 9 **33%** 0.21 to 0.47 13 7 0	5 13 **60%** 0.50 to 0.71 8 4 0

Table 3: Objective tumor response in both arms.

however uncommon except for neutropenia. In particular, the adverse events that occurred significantly more often in patients who received FOLFOXIRI were grade 2 to 3 neurotoxicity (0% vs. 20%; p < 0.0001) and grade 3 to 4 neutropenia (26.6% vs. 53.3%; p = 0.0001). Febrile neutropenia was comparable between FOLFIRI and FOLFOXIRI (3.3% vs. 6.6% of patients; p = 0.2), and granulocyte colony-stimulating factor was used in 5% of FOLFIRI cycles and in 10% of FOLFOXIRI cycles. In two patients oxaliplatin was interrupted because of grade 3 neurotoxicity (n = 1) or allergic reaction (n = 1).

Objective tumor response

According to an intention–to–treat analysis, all patients were considered assessable for response (Table 3). The RR assessed was 60% (18/30) for FOLFOXIRI and 33% for FOLFIRI (p = 0.007). Moreover, the rate of progression was significantly lower for patients treated with FOLFOXIRI (11% vs. 24%, p = 0.02). In the multivariate analysis, only treatment with FOLFOXIRI was an independent predictive factor for response (hazard ratio [HR], 2.0; 95% CI, 1.2 to 2.8; p < 0.001).

Secondary surgery on metastases

The superior tumor shrinkage achieved with FOLFOXIRI allowed an increased rate of post chemotherapy radical surgery of metastases. From eighteen patients, 5 patients (16.66%) underwent to radical (RO) surgery of metastases in the FOLFOXIRI arm compared with one patient (3.33%) in the FOLFIRI arm (p = 0.02). In the multivariate analysis, only treatment with FOLFOXIRI was an independent predictive factor for achieving an RO resection (HR, 2.8; 95% CI, 1.2 to 5.9; p = 0.018).

PFS

The improved activity of FOLFOXIRI resulted in an increased PFS; with median PFS of 10 months vs. 7.5 months (p = 0.0099) with an HR for progression of 2.58 (95% CI, 1.2 to 5.3). In addition, the rate of early progression (patients who progressed within 6 months from the treatment onset) was significantly lower in the FOLFOXIRI arm (18% vs. 45%; p < 0.0001).

The Cox's multivariate analysis demonstrates that independent prognostic factors for reduction of the progression risk were: treatment arm (2.58; 95% CI, 1.2 to 5.3; p = 0.0099), male sex (HR, 0.61; 95 CI, 0.50 to 0.89; p = 0.01) and leukocyte count less than 2500/mm^3 (HR, 0.59; 95% CI, 0.44 to 0.79; p = 0.0027). PFS of both treatment arms is represented in (Figure 1).

OS

After a median follow up of 18.4 months, the median OS was significantly longer for FOLFOXIRI (22.6 vs. 16.7 months; p = 0.032), corresponding to an HR for death of 0.70 (9.5% CI, 0.50 to 0.96; Figure 2). The Cox's multivariate analysis demonstrates that the only independent prognostic factors for reduction of the death risk was liver involvement less than 25% (HR, 0.57; 95% CI, 0.39 to 0.84; p = 0.005).

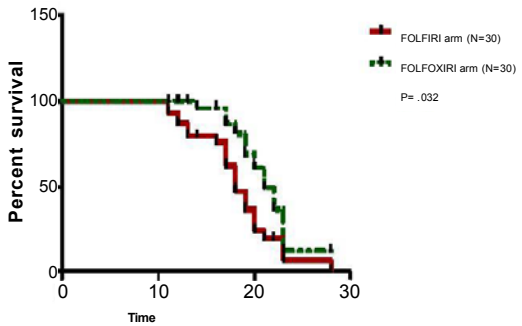

Figure 1:

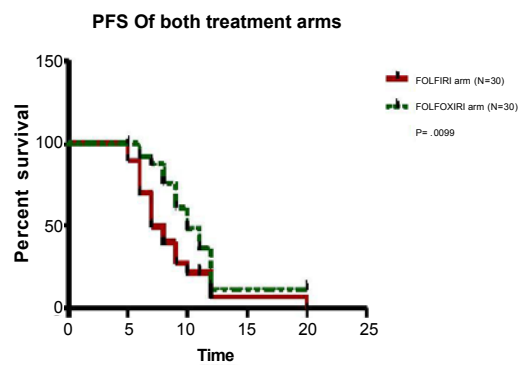

Figure 2:

Treatment with FOLFOXIRI was significantly predictive of prolonged survival in the univariate analysis (p = 0.032) but in the multivariate analysis, it was borderline significant (p = 0.054). OS of both treatment arms is represented in (Figure 2).

Discussion

During recent years, the treatment of metastatic colorectal cancer has achieved considerable progress, mainly improvements in the efficacy of chemotherapy, for increased use of surgery on metastases [11]. FOLFOXIRI has been compared with FOLFIRI in 2 randomized clinical trials in unresectable patients [9,10]. In both studies, FOLFOXIRI led to an increase in RO secondary resection rates: 6% vs. 15% p = 0.033 in the Gruppo Oncologico Nord Ovest (GONO) trial [9], with significant improvement in the response rate (34% vs. 60%, p < 0.0001), and both PFS (6.9 vs. 9.8 months; HR, 0.63; p = 0.0006), and median overall survival (16.7 vs. 22.6 months; HR, 0.70; p = 0.032). In the (GONO) trial there were increased tendency for toxicity, with significantly higher grade 2 and 3 neurotoxicity (28% vs. 50%; p < 0.001), grade 3 and 4 neutropenia (3% vs. 5%), and grade 3 to 4 diarrhea (12% vs. 20%). In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median overall survival of 23.4 vs. 16.7 months (p = 0.026) [12]. Response rate, survival, and toxicity profile were comparable in our study.

In the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial (10) RO resection rate was improved with FOLFOXIRI than FOLFIRI 4% vs. (10%, p = 0.08). Response rate is 33.6% vs. 43%, p = 0.168 in favor of FOLFOXIRI. Overall survival and median PFS were also higher in FOLFOXIRI arm (19.5 vs. 21.5 months; p = 0.337), (6.9 vs. 8.4 months; p = 0.17) respectively. Patients treated with FOLFOXIRI had a significantly higher incidence of alopecia (p = 0.0001), diarrhea (p = 0.0001) and neurosensory toxicity (p = 0.001) compared with patients treated with FOLFIRI. Response rates were comparable to our results especially FOLFIRI arm, both median OS and PFS were comparable to our results.

In our present trial we used a biweekly schedule without administration of FU by intravenous bolus as in FOLFIRI to deliver elevated dose intensities of CPT-11, Oxaliplatin, and infusional FU. Results obtained in the FOLFIRI arm are in line with those reported in most other randomized trials [11-17]. FOLFOXIRI results demonstrate that toxicities are moderately increased, mainly neurotoxicity and neutropenia but this combination remains feasible and well tolerated. In our study FOLFOXIRI increased RR clearly.

This improved activity allowed a significant increase in the rate of radical secondary surgery of metastases, and the rate of RO patients achieved with FOLFOXIRI was particularly impressive in patients with liver metastases only (3% vs. 16%; p = 0.02).

Treatment with FOLFOXIRI was the only significant independent predictive factor for obtaining an objective response on an RO resection. The improved activity of FOLFOXIRI resulted in an increased PFS; with median PFS of 10 months vs. 7.5 months (p = 0.0099) with an HR for progression of 2.58 (95% CI, 1.2 to 5.3). In addition, the rate of early progression was significantly lower in the FOLFOXIRI arm (18% vs. 45%; p < 0.0001).

The addition of targeted therapy definitely added to the management of advanced colorectal carcinoma. Bevacizumab was compared when added to IFL regimen vs. IFL and placebo, a phase III trial that randomly assigned 813 patients; 402 to receive (IFL) plus bevacizumab (5 mg per kilogram of body weight every two weeks) and 411 to receive IFL plus placebo. The median duration of survival was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 (p < 0.001). The median PFS was significantly higher for bevacizumab (10.6 months compared to 6.2 months), (HR for disease progression, 0.54; p < 0.001); the RR also was significantly higher with addition of bevacizumab (44.8 % and 34.8%, p = 0.004). Grade 3 hypertension was more common during treatment with bevacizumab (11.0 % vs. 2.3 %) but was easily managed [18].

The efficacy of cetuximab plus FOLFIRI as first-line treatment for metastatic colorectal cancer was tested against FOLFIRI alone, and the mutation status of the KRAS gene was correlated with the clinical response to cetuximab. The primary end point was progression-free survival. A total of 1,198 patients were equally randomly assigned into two arms, one received cetuximab plus FOLFIRI, and the other arm received FOLFIRI alone. The overall survival was not different between the two treatment groups (hazard ratio, 0.93; 95% CI, 0.81 to 1.07; p = 0.31). The hazard ratio for progression-free survival in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.85 (95% confidence interval [CI], 0.72 to 0.99; p = 0.048). KRAS mutation significantly affected response rate (p = 0.03) with no significant effect on either OS (p = 0.44), or PFS (p = 0.07). The hazard ratio for progression-free survival among patients with wild-type–KRAS tumors was 0.68 (95% CI, 0.50 to 0.94), in favor of the cetuximab–FOLFIRI group. Grade 3 or 4 adverse events were more frequent with cetuximab plus FOLFIRI than with FOLFIRI alone: skin reactions (which were grade 3 only) (in 19.7% vs. 0.2% of patients, p < 0.001), infusion-related reactions (in 2.5% vs. 0%, p < 0.001), and diarrhea (in 15.7% vs. 10.5%, p = 0.008). It was concluded that only KRAS wild type tumors had reduced risk of progression with cetuximab therapy [19].

In another study, patients with metastatic colorectal cancer previously treated with a fluoropyrimidine regimen were randomly assigned to FOLFIRI or FOLFIRI plus panitumumab. Patients with KRAS wild-type tumors experienced a statistically significant PFS advantage (HR, 0.73; 95% CI, 0.59–0.90; p = 0.004, stratified log-rank). Median PFS was 5.9 months (95% CI, 5.5-6.7) for panitumumab-FOLFIRI and 3.9 months (95% CI, 3.7 months–5.3 months) for FOLFIRI alone. Panitumumab did not significantly affect OS or PFS in patients with mutant KRAS tumors [20].

In an open, multicentre randomized phase 2 study that examined the effectiveness of cetuximab and either FOLFOX6 (group A) or FOLFIRI (group B) in neoadjuvant treatment of unresectable colorectal liver metastases (CELIM trial), high tumour-response rates were achieved with cetuximab and either FOLFIRI or FOLFOX6. This translated into a high rate of metastasectomy. RR was highest in KRAS wild-type tumors. Objective tumour response was noted in 66 (62%, 95% CI 52–72) of 106 patients, with a non-significant difference of 11% (95% CI –8 to 30, p = 0·23) between both groups. Tumour response was similar in EGFR-detectable and EGFR-undetectable tumors. R0 resections were achieved in 36 of 106 patients (34%, 95% CI 25–44), 20 (38%) of 53 in group A, and 16 (30%) of 53 patients in group B. R0 or R1 resection and/or radiofrequency ablation was done in 49 (46%) of 106 patients [21]. Of course resectability rate in this study was higher than our study since only patients with potentially resectable liver metastases were included yielding higher rate of response and resectability. Multidisciplinary approach together with the advances in both surgical techniques and systemic therapy, including both chemotherapy and biological agents has lead to significant improvement in survival with

increased rate of surgical metastasectomy. However with the higher cost of the biological agents, considering cost-effectiveness relationship, FOLFOXIRI represents a combination that is superior to an infusional FU containing doublet compared to FOLFIRI, with improved efficacy, coupled with a manageable toxicity profile, and comparable to biological agents. Our results support the use of FOLFOXIRI as a first line option of care for selected patients with metastatic colorectal cancer. We do recommend FOLFOXIRI to be tested in neodjuvant setting in initially unresectable (potentially resectable) patients and perhaps in patients with few chances to achieve a three drug exposure in a sequential strategy.

References

1. Siegel R, Ward E, Brawley O, Jemal A (2011) Cancer Statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61: 212-236.
2. Cheng L, Eng C, Nieman LZ, Kapadia AS, Du XL (2011) Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. Am J Clin Oncol 34: 573-580.
3. Lee WS, Yun SH, Chun HK, Lee WY, Yun HR, et al. (2007) Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. Int J Colorectal Dis 22: 699-704.
4. Van Cutsem E, Nordlinger B, Adam R, Köhne CH, Pozzo C, et al. (2006) Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer 42: 2212-2221.
5. Yoo PS, Lopez-Soler RI, Longo WE, Cha CH (2006) Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. Clin Colorectal Cancer 6: 202-207.
6. Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, et al. (2005) Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. J Clin Oncol 23: 9243-9249.
7. Kemeny N (2006) Management of liver metastases from colorectal cancer. Oncology (Williston Park) 20: 1161-1176, 1179.
8. Muratore A, Zorzi D, Bouzari H, Amisano M, Massucco P, et al. (2007) Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? Ann surg Oncol 14: 766-770.
9. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, et al. (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 25: 1670-1676.
10. Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, et al. (2006) FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J cancer 94: 798-805.
11. Gill S, Goldberg RM (2004) First-line treatment strategies to improve survival in patients with advanced colorectal cancer. Drugs 64: 27-44.
12. Masi G, Vasile E, Loupakis F, Cupini S, Fornaro L, et al. (2011) Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst 103: 21-30.
13. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, et al. (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355: 1041-1047.
14. Tournigand C, André T, Achille E, Lledo G, Flesh M, et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22: 229-237.
15. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, et al. (2005) Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol 23: 4866-4875.
16. Seymour MT (2005) Fluorouracil, Oxaliplatin and CPT-11 (irinotecan), Use and sequencing (MRC FOCUS): a 2135-patient randomized trial in advanced colorectal cancer (ACRC). J Clin Oncol 23: 165S.
17. Labianca R, Sobrero A, Isa L, Cortesi E, Barni S, et al. (2011) Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. Ann Oncol 22: 1236-1242.
18. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, et al. (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350: 2335-2342.
19. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, et al. (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360: 1408-1417.
20. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, et al. (2010) Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 28 : 4706-4713.
21. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, et al. (2010) Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 11: 38-47.