Farm Hosp. 2009;**33(2):**89-95

Farmacia
HOSPITALARIA

www.elsevier.es/farmhosp

ORIGINAL ARTICLE

Therapeutic use and profile of toxicity of the FOLFOX4 regimen☆

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Received August 11, 2008; accepted January 20, 2009

KEYWORDS
FOLFOX4;
Toxicity;
Usage study

Abstract
Introduction: Since the publication of the MOSAIC test results in 2004, the FOLFOX4 regimen has been established as an adjuvant treatment which is recommended in stage III colorectal cancer. The aim of this study is to assess the use of this regimen in our field and to describe its toxicity.
Methods: Descriptive study of treatments with FOLFOX4 prescribed between April 2005 and March 2007. The data was obtained from the Farhos Oncología® programme and clinical records. The following data was collected: age, gender, diagnosis, stage of the illness (TNM classification), and adverse reactions, expressing severity according to Common Toxicity Criteria 2.0.
Results: The FOLFOX4 regimen was prescribed for 39 patients (24 men and 15 women) with an average age of 59. The diagnoses were: 28 colon cancer (4 stage II, 17 stage III, and 7 stage IV), 10 rectal cancer (1 stage II, 4 stage III, and 5 stage IV), and 1 stage IV gastric cancer. The most frequent adverse reactions were peripheral neuropathy (82%), neutropaenia (56.4%), and diarrhoea (53.9%). When the study was completed, 9 patients continued active treatment with the regimen (average, 6.8 cycles). Of the 30 remaining patients only 16 people completed the 12 planned cycles. Forteen patients stopped their treatment (average, 8.1 cycles) due to toxicity in 10 cases, clinical progression in 3 cases, and 1 patient died. Of the total 368 cycles administered, 68 suffered administration delays and 22 had the dosage reduced.
Conclusion: The use of the FOLFOX4 regimen has been adjusted to uses with some solid scientific evidence, but its toxicity has limited its use and has made administering the planned dosage levels difficult.

☆The preliminary results of this study were presented in the 51st National Congress of the SEFH (Spanish Society of Hospital Pharmacists), held in Málaga on September 26 to 29, 2006.

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PALABRAS CLAVE
FOLFOX4;
Toxicidad;
Estudio de utilización

Uso terapéutico y perfil de toxicidad del esquema FOLFOX4

Resumen

Introducción: Desde la publicación de los resultados del estudio MOSAIC en 2004, el esquema FOLFOX4 se ha establecido como un tratamiento adyuvante recomendado en los cánceres colorrectales estadio III. El objetivo de este estudio es valorar la utilización de este esquema en nuestro ámbito y describir su toxicidad.

Métodos: Estudio descriptivo de los tratamientos con FOLFOX4 prescritos desde abril de 2005 a marzo de 2007. Los datos se obtuvieron del programa Farhos Oncología® y las historias clínicas. Se recogieron las variables siguientes: edad, sexo, diagnóstico, estadio de la enfermedad (clasificación TNM) y reacciones adversas, expresando su gravedad según los Common Toxicity Criteria 2.0.

Resultados: El esquema FOLFOX4 ha sido prescrito a 39 pacientes (24 varones y 15 mujeres), con una mediana de edad de 59 años. Los diagnósticos fueron: 28 cáncer de colon (4 estadio II, 17 III y 7 IV), 10 cáncer de recto (1 estadio II, 4 III y 5 IV) y 1 cáncer gástrico estadio IV. Las reacciones adversas más frecuentes fueron neuropatía periférica (82%), neutropaenia (56,4%) y diarrea (53,9%). Al finalizar el estudio 9 pacientes seguían en tratamiento activo con este esquema (media, 6,8 ciclos). De los 30 restantes, sólo 16 completaron los 12 ciclos previstos. En 14 pacientes se suspendió el tratamiento (media, 8,1 ciclos), siendo los motivos: toxicidad en 10 casos, progresión clínica en 3 y fallecimiento en 1. Del total de los 368 ciclos administrados, 68 tuvieron retrasos en la administración y en 22 se redujo la dosis.

Conclusión: La utilización del esquema FOLFOX4 se ha ajustado a usos con unas evidencias científicas sólidas, pero su toxicidad ha limitado el uso y dificultado la administración de la intensidad de dosis prevista.

Introduction

Colorectal cancer (CRC) ranks at second place in terms of incidence and mortality due to cancer in the majority of developed countries, both for men and women; when both sexes are considered together, this neoplasia ranks at first place.[1]

In Spain, in 2000, there were 5951 deaths due to CRC in men and 5001 in women, representing 11%of deaths due to cancer in men and 15%in women. The number of new cases per year is estimated at around 21 000 in both sexes.[2]

The most important prognosis factor for survival of CRC is the stage of the disease at the time of diagnosis.[3] Consequently, patients diagnosed at stage I have a rate of survival at 5 years higher than 90%, while in the case of those diagnosed at stage IV, this rate is reduced to less than 10%.[4]

Chemotherapy treatment of metastatic CRC has been based for over 4 decades on 5-fluorouracil (5-FU), also known as fluoropyrimidine, which acts by inhibiting thymidylate synthase. The activity of this drug in monotherapy was insubstantial; therefore various strategies were developed to increase its efficacy.[5]

Association of 5-FU and leucovorin (LV) demonstrated a significant increase in the response rates and a small improvement in total survival with respect to monotherapy with 5-FU.[6]

Another strategy to increase the activity of 5-FU, whose half-life is short, consisted of extending the perfusion time. This strategy demonstrated, in a meta-analysis carried out at the end of the nineties, a statistically significant increase, albeit modest, in total survival, as well as an improved profile of toxicity, with fewer incidences of myelosuppression, although there was a higher frequency of palmoplantar erythrodysesthesia.[7]

In other studies, 5-FU has been replaced with its oral prodrug, capecitabine, with similar results.[8,9]

Treatment of metastatic CRC has changed since the appearance of irinotecan and oxaliplatin.[10] Irinotecan has been studied in various combinations with 5FU/LV, administered in bolus[11] and in continuous perfusion,[12-14] showing advantages in the rates of response, disease-free survival and total survival, especially with continuous perfusion of 5-FU.

The FOLFOX4 regimen, formed by adding oxaliplatin to 5-FU/LV in perfusion, used as a first course of treatment for metastatic CRC, demonstrated an increase in the response rate, in disease-free survival and total survival. However, in the latter case, the difference was not statistically significant.[15] This regimen has shown a time span until progression, and total survival, similar to that of the FOLFIRI regimen[16] and higher than the IFL regimen as a first course of treatment.[17]

It has not yet been established which of the 2 drugs should be used as a first course of treatment for the metastatic disease, despite the various comparative studies which have been undertaken,[16-18] therefore it is the profile of toxicity of each regimen which conditions the individual choice of the patient.[19] The main guidelines reflect this.[20-22]

The meta-analysis carried out by Grothey et al,[23] which analysed the results of 7 clinical tests in phase III of metastatic CRC, concluded that total survival has a

significant correlation with the percentage of patients who end up taking the 3 drugs (5-FU, irinotecan and oxaliplatin) during the course of the disease.

The FOLFOX4 regimen could be one of the alternative means of treatment, both as a first and a second course of treatment of the metastatic disease.

In the context of adjuvant treatment, Moertel et al[24] treated patients with stage III colon cancer with the combination of 5-FU/levamisole, and demonstrated, for the first time, a reduction of 33% in mortality. Due to these results, various studies were undertaken, which established 6 months of treatment with 5-FU/LV as standard adjuvant chemotherapy treatment for stage III CRC.[25,26]

Following the encouraging results obtained with respect to metastatic disease, the combinations of 5FU/LV plus oxaliplatin or irinotecan have been evaluated as adjuvant treatment for CRC. While the studies with irinotecan have not represented an improvement on the previous results,[27] the FOLFOX4 regimen has been the first combination which has demonstrated a significant improvement in this context. In the MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) study[28] the rate of disease-free survival at 3 years was statistically higher compared with the classic Mayo Clinic (5FU/LV bolus) regimen.

Since the publication of the results of the MOSAIC study in 2004, the FOLFOX4 regimen has been established as one of the recommended adjuvant treatments for CRC diagnosed at stage III. However, the FOLFOX4 regimen is an aggressive treatment that has greater toxic effects, which mainly consist of sensory peripheral neuropathy and neutropaenia, which may limit its use.[28]

Within this context, the objectives of our study are:

- To assess the usage profile of the FOLFOX4 regimen within our environment, with respect to published scientific evidence
- To describe its profile of toxicity in daily health care usage and its relationship with the completion of the treatment plan

Methods

A descriptive study was designed for the patients in treatment with the FOLFOX4 regimen in our hospital, during the period between April 2005 and March 2007, with the follow-ups of all cycles administered in this period.

The FOLFOX4 regimen is formed by oxaliplatin 85 mg/m^2, administered on day 1, plus 5-FU at a dosage of 400 mg/m^2 administered in bolus form, followed by 600 mg/m^2 administered in continuous perfusion during a 22-h period, modulated by LV 200 mg/m^2 on days 1 and 2. The data for the follow-up of the patients was obtained with the Farhos Oncología® program and from the clinical histories. The following variables were recorded: age, sex, diagnosis, stage of the disease according to the TNM[3] classification, and adverse reactions experienced during treatment, with its severity expressed according to the Common Toxicity Criteria version 2.0.[29]

A follow-up sheet was designed individually for each patient, in which all of the adverse reactions recorded during each cycle of treatment were listed, together with their degree of severity. Details of which of these reactions caused, or were associated with, delays in administration of the cycle of treatment, a reduction in the dosage of the drugs which form the FOLFOX4 regimen and/or the definitive discontinuity of the treatment, were recorded as appropriate.

Results

During the 2 years of the study, the FOLFOX4 regimen was prescribed to 39 patients (24 men and 15 women), with ages between 37 and 75 years and an average age of 59 years. The number of patients, itemised by years, was 23 the first year (from April 2005 until March 2006) and 16 the second (from April 2006 until March 2007).

The diagnoses in which the regimen were used were: 28 colon cancer (4 stage II, 17 stage III, and 7 stage IV), 10 rectal cancer (1 stage II, 4 stage III, and 5 stage IV), and 1 stomach cancer stage IV.

Of the 5 patients diagnosed with CRC stage II, 4 displayed poor prognosis factors: in 2 T4 cases, in 1 T4 case with perforation, and only 7 lymph nodes analysed, and in the fourth patient the persistence of a rising CEA marker after surgery. In the clinical history of one of the patients it appeared that there was no remaining risk factor.

During the study period, the 39 patients received a total of 368 cycles.

In Table 1, the episodes of toxicity are shown which were recorded more frequently during the follow-ups of the patients. Other adverse reactions observed less frequently were: abdominal pain on 7 occasions; an alteration in taste, alopecia, and rectal bleeding in 5; respiratory infection, fever, and visual alterations in 3; constipation, pemphigus, epistaxis, and urinary infection in 2, and alterations of the skin, bone pain, ungueal toxicity, flu, oesophagitis, increase of the hepatic enzymes, and hypersensitivity reaction to oxaliplatin only in 1.

The incidence of the main toxicities in the patients is detailed in Table 2, which states the percentage of patients who developed the adverse effect, only in the greatest degree reached during the entire treatment. As regards the completion of the scheduled treatment regimen, the following results were observed:

- At the end of the study period 9 patients were continuing active treatment with the FOLFOX4 regimen, with an average of 6.8 cycles administered per patient
- Of the 30 patients who were no longer under active treatment with this regimen, only 16 had completed the 12 scheduled cycles (53.3%). In 14 patients the treatment was discontined (average cycles administered per patient, 8.1), the reasons for discontinuity were: toxicity in 10 cases, clinical progression in 3; and the death of 1 patient

The adverse reactions which resulted in the discontinuity of the treatment were: in 7 patients, neurological toxicity; in 1, complications with the reservoir with extravasation of liquid and infection with coagulase + *Staphylococcus*; in 1 significant hyporexia; and in 1, hypersensitivity reaction to oxaliplatin.

Table 1 Episodes of toxicity documented during the study period

Adverse reaction	Stage 1	Stage 2	Stage 3	Stage 4	Total number
Neutropaenia	16	29	15	2	62
Thrombopaenia	9	3	2	—	14
Leukopaenia	—	2	—	—	2
Haemoglobulinaemia	—	8	—	1	9
Peripheral neuropathy		28	2	—	133
Nausea	22	8	—	—	30
Vomiting	9	—	-	—	9
Diarrhoea	28	16	1	—	45
Asthenia	17	14	—	—	31
Mucositis	13	4	—	—	17
Hyporexia	8	—	1	—	9

Table 2 Percentage of patients who developed toxicity in according to the highest degree shown during treatment

Adverse reaction	Stage 1	Stage 2	Stage 3	Stage 4	Total percentage
Neutropaenia	10.3	17.9	23.1	5.1	56.4
Thrombopaenia	10.3	5.1	5.1	—	20.5
Leukopaenia	—	2.6	—	—	2.6
Haemoglobulinaemia	—	5.1	—	2.6	7.7
Peripheral neuropathy	35.9		5.1	—	
Nausea	23.1	12.8	—	—	35.9
Vomiting	20.5	—	—	—	20.5
Diarrhoea	20.5	30.8	2.6	—	53.9
Asthenia	17.9	15.4	—	—	33.3
Mucositis	17.9	5.1	—	—	
Hyporexia	12.8	—	2.6	—	15.4

Table 3 Adverse reactions associated with delays of cycles and reductions of dosage

Toxicity	Lateness (ADJ/M+)	Reductions (ADJ/M+)
Neutropaenia	40 (29/11)	
Thrombopaenia	13 (12/1)	—
Haemoglobulinaemia	4 (3/1)	—
Leukopaenia	1 (1/0)	—
Peripheral neuropathy	13 (13/0)	7 (6/1)
Diarrhoea	3 (3/0)	1 (1/0)
Asthenia	3 (2/1)	—
Nausea	2 (2/0)	—
Urinary infection	1 (1/0)	—
Bone pain	1 (0/1)	—
Mucositis	1 (1/0)	2 (2/0)
Pemphigus	1 (1/0)	—
Total	83 (68/15)	22 (18/4)

ADJ indicates adjuvant treatment; M+, metastatic disease.

Of the total of 368 cycles administered, 68 (18.47%) underwent delays in administration (29 patients were affected) and in 22 (5.97%) the dosage was reduced (15 patients underwent some reduction). The reasons are detailed in Table 3. Together, only 9 patients did not undergo delays or reduction of dosage in their treatment. If we consider the 16 patients who received the 12 cycles during the study, only 3 did so without incidences.

In terms of the completion of the treatment for the 26 patients who received it as adjuvant treatment, the results are as follows: 14 patients received the 12 scheduled cycles, 5 remained under treatment at the end of the study and 7 discontinued treatment before its completion, all of whom due to toxicity. In addition, in 22 patients (56.41%) the administration of a cycle was delayed (in total 56 cycles) and 11 (28.20%) underwent some reduction of dosage (18 cycles in total). The reasons are also described in Table 2. Of the 14 patients who completed the adjuvant treatment, only 1 was not subject to any delay or reduction of the dosage.

Discussion

The predominance of men in our study is consistent with the greater incidence and prevalence of CRC reported among males.[2]

In our hospital centre, the FOLFOX4 regimen has mainly been prescribed as adjuvant treatment for CRC. Its use as an adjuvant in colorectal tumours diagnosed at stage III (locoregional lymph nodes affected) is widely documented, based mainly on the results of the MOSAIC study.[28] This latest

update of the results of this study, presented in the ASCO Congress 2007,[30] maintains the advantage to patients treated with FOLFOX4 in terms of survival without progression at 5 years. The details of total survival at 6 years show a significant increase for the group of patients with stage III. This regimen is currently considered one of the most recommended treatments for stage III.[20,31]

For patients diagnosed at stage II there is still controversy as regards the use or otherwise of adjuvant treatment, since the margin of absolute benefit in survival is low, between 1% and 5%[32-35] While studies are being undertaken to assess molecular markers which assist the identification of which patients would benefit from the treatment,[36] the most accepted reccommendation is to offer adjuvant treatment to patients with stage II who display some factor of poor prognosis. The most accepted factors are: size of tumour T4 or intestinal obstruction, perforation, poorly distinguished tumour, less than 10 lymph nodes examined, and/or lymphovascular peritumoral invasion.[20,37]

In 3 of our patients treated with the adjuvant FOLFOX4 regimen in stage II, 1 or more of these risk factors were identified; in the fourth patient treatment was initiated due to persistent raising of the CEA marker following surgery, which could be indicative of a hidden disease. In the fifth patient, the clinical history did not reflect any of these factors.

The use of the regimen in metastatic CRC is also well established in view of the studies of de Gramont et al[15] and the subsequent comparisons with other active regimens.[16,17]

The use, in a patient with stage IV gastric carcinoma is based on the study of Cavanna et al,[38] which concluded that FOLFOX4 is a regimen with an activity comparable to other regimens used for this pathology, and it is well tolerated.

As regards the profile of toxicity found in our patients, the onset of sensory peripheral neuropathy is noteworthy. This is an adverse effect widely described with the use of oxaliplatin, which has a dual presentation: it causes acute peripheral neuropathy and late-onset peripheral neuropathy, which increases in intensity depending on the cumulative dosage. It even persists between chemotherapy cycles. In the MOSAIC[28] study the safety results of the FOLFOX4 regimen showed that 92% of patients had peripheral neuropathy, 12% classified as grade 3. In our study, during the follow-up of the adverse reactions, peripheral neuropathy was reported in 82.05% of patients, with 5% grade 3. Other studies undertaken on metastatic disease describe variable incidences of peripheral neuropathy, related with the number of cycles administered. Consequently, de Gramont et al[15] described 68% of total incidence and 18% of grades 3-4, with an average of 12 cycles administered per patient; Colucci et al[16] found 45% incidence, with 4% of grades 3-4, but with an average of 8 cycles administered per patient.

The results of our study may be prepared from a less exhaustive record, especially in terms of the reactions associated with perfusion which take place after the medical examination; in addition, it must be borne in mind that both patients under adjuvant treatment and patients with metastatic disease were included and were not subject to the selection criteria of a clinical test. In addition, 9 patients were included who were still under treatment, which could result in higher levels of toxicity, given that it is cumulative.

One of the limitations of the study is that the source of information is not the direct interview with the patient but the clinical history record. This source could be a contributing factor to the different incidences found in some of the adverse effects.

Haematological toxicity was also relevant, with the noteworthy onset of neutropaenia, which affected 56.4% of our patients to a greater or lesser degree. It must be borne in mind that the incidence of grade 3-4 neutropaenia was 28.1%, a level considerably lower than that recorded in the MOSAIC study,[28] in which the incidence was 41%, and in the studies of de Gramont et al[15] (41.7%) and of Goldberg et al[17] (50%). Only the study of Colucci et al[16] describes a similar incidence (28%).

Thrombopaenia is an adverse effect frequently associated with the administration of regimens with oxaliplatin. Although the total incidence was less than other studies (20.5% compared with 77.4% of the MOSAIC study,[28] 76.2% of de Gramont et al,[15] and 43% of Colucci et al[16]), the 5.1% of grade 3 is noteworthy, which is considerably higher than other publications (1.7%,[28] 2.5%,[15] and 3%[16]).

The third relevant site of toxicity is the gastrointestinal tract. Diarrhoea and mucositis are more related with the administration of 5-FU, especially in continuous perfusion, as is the case with the FOLFOX4 regimen. Nausea, vomiting, and asthenia are related with both drugs. The incidences of nausea, vomiting, and mucositis are much less than those described in the MOSAIC study, while the total incidence of diarrhoea is similar in our study, although with a less significant onset of grades 3 and 4.

Among the adverse reactions of less incidence, it is significant that in one patient the regimen was discontinued due to hypersensitivity to the oxaliplatin perfusion. In the bibliography several cases have been documented.[15,16,28,39]

The completion of the treatment programme was poor, mainly due to the toxicity of the regimen, as observed in the reductions of dosages and delays in the administration of the treatment. This is important mainly in the scope of adjuvant treatment, where the intention of the treatment is curative; in our study 66.7% of the patients completed the 12 scheduled cycles of adjuvant treatment, compared with 74.7% in the MOSAIC study; in addition, only one patient completed them without delays or reductions in dosages.

During the second year of the follow-up period a decrease was observed in the number of patients treated with the FOLFOX4 regimen; this fact may be due to various factors:

- Firstly, as has been observed in our results, the cumulative toxicity of the regimen. It must also be borne in mind that it is a complex regimen in terms of its administration and requires the implantation of a reservoir for continuous perfusion of 5-FU. In immunodepressed patients this reservoir is a potential centre of infection and other complications, which some researchers have estimated at between 15% and 20%.
- Another factor which may have influenced the reduction of the prescription of FOLFOX4 was the appearance of the results of the comparative studies with the XELOX regimen (oxaliplatin IV associated with capecitabine oral in cycles of 21 days). In the context of the former (phase III NO16.966)[40] and second (phase III NO16.967)[41] courses of the metastatic disease the XELOX regimen has demonstrated non-inferiority

compared with FOLFOX4 in terms of survival without progression, and was equivalent in total survival. As regards the profile of toxicity, XELOX causes a higher incidence of palmoplantar erythrodysesthesia and diarrhoea, but less grade 3-4 neutropaenia than FOLFOX4. The incidence of neuropathy is similar with both regimens

In the context of adjuvant therapy, no comparative studies have been published between both regimens. Indeed, there are comparative studies of capecitabine compared with 5-FU/LV,[42] with similar efficacy results, and of XELOX compared with 5-FU/LV with acceptable toxicity, although the efficacy data is still not known.[43] Together, the availability of similar efficacy data with respect to metastatic disease, together with its greater convenience of administration and a manageable profile of toxicity, it has encouraged many clinics to use this regimen as adjuvant treatment, even in the absence of results of specific studies.

To conclude, the use of the FOLFOX4 regimen has generally been adapted to uses with solid scientific evidence, but its profile of toxicity has limited its use and has made difficult the administration of an anticipated intensity of dosage, ultimately resulting in a reduction in the total use of the regimen.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide, 10th ed. Lyon: IARC Press; 2001.
2. La situación del Cáncer en España. Ministerio de Sanidad y Consumo, 2005 [cited, Jun 20, 2008] Available from: http://www.isciii.es/htdocs/centros/epidemiologia/epi_cancer.jsp
3. Colon and rectum. In: American Joint Committeé on Cancer. AJCC cancer staging manual. 5th ed. Philadedlphia: Lippincott-Raven; 1997. p. 83-90.
4. American Cancer Society. Colon and rectum cancer [cited, Jun 20,2008]. Available from: http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_colon_and_rectum_cancer_staged.asp
5. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med. 2005;352:476-87.
6. Meta-Analysis Group in Cancer. Modulation of fl uorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. J Clin Oncol. 2004;22:3766-75.
7. Meta-Analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol. 1998;16:301-8.
8. van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol. 2001;19:4097-106.
9. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol. 2001;19:2282-92.
10. Folprecht G, Köhne CH. The role of new agents in the treatment of colorectal cancer. Oncology. 2004;66:1-17.
11. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343:905-14.
12. Andre T, Louvet C, Maindrault-Goebel F, Couteau C, Mabro M, Lotz JP, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer. 1999;35:1343-7.
13. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet. 2000;355:1041-7.
14. Kohne CH, van Cutsem E, Wils J, Bokemeyer C, El-Serafi M, Lutz MP, et al. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. J Clin Oncol. 2005;23:4856-65.
15. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938-47.
16. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. 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. 2005;23:4866-75.
17. Goldberg R, Sargent D, Morton R, Fuchs C, Ramanathan R, Williamson S, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22:23-30.
18. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study. J Clin Oncol. 2004;22:229-37.
19. Díez-Fernández R, Salinas P, Girón-Duch C. Revisión del tratamiento quimioterápico del cáncer de colon metastático. Farm Hosp. 2006;30:359-69.
20. National Comprehensive Cancer Network: Practice Guidelines in Oncology, Colon Cancer [cited, Jun 20, 2008]. Available from: http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf
21. The role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first and second-line treatment of advanced colorectal cancer: A clinical practice guideline [cited, Jun 20, 2008]. Available from: http://www.cancercare.on.ca/english/toolbox/drugs/drugformulary/drugregimens/gastro/#coloadv
22. Colon Cancer Treatment (PDQ®). National Cancer Institute [cited, Jun 20, 2008]. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page10
23. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan and oxaliplatin in the course of treatment. J Clin Oncol. 2004;22:1209-14.
24. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med. 1990;322:352-8.
25. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet. 1995;345:939-44.
26. Wolmark N, Rockette H, Mamounas E, Jones J, Wieand S, Wickerham DL, et al. Clinical trial to assess the relative effi cacy of fluorouracil and lecovorin, fluorouracil and levamisol, and fluorouracil, leucovorin, and levamisol in patients with

Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project protocol C-04. J Clin Oncol. 1999;17:3553-9.
27. Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol. 2007;25:3456-61.
28. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350: 2343-51.
29. National Cancer Institute Common Toxicity Criteria version 2.0 [cited, Jun 20, 2008]. Available from: http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf
30. de Gramont A, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Oxaliplatin/5FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years. J Clin Oncol. 2007;25 Suppl 20:abstract 4007.
31. Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: Guideline Recommendations [cited, 20 Jun 2008]. Available from: http://www.cancercare.on.ca/english/toolbox/drugs/drugformulary/drugregimens/gastro/#coloadj
32. Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ; Quasar Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370:2020-9.
33. Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, et al. Comparative efficacy of adjuvant chemotherapy in patients with Duke's B versus Duke's C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies (C-01, C-02, C-03 and C-04). J Clin Oncol. 1999;17:1349-55.
34. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J Clin Oncol. 1999;17:1356-63.
35. Gill S, Loprinzi CL, Sargent DJ, Thomé SD, Alberts SR, Haller DG, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol. 2004;22:1797-806.
36. Aranha O, Benson AB 3rd. Adjuvant therapy for colon cancer. Curr Gastroenterol Rep. 2007;9:415-21.
37. Aranda E, Abad A, Carrato A, Cervantes A, Tabernero J, Díaz-Rubio E; TTD Group (Spanish Cooperative Group for Gastrointestinal Tumor Theraphy). Guides for adjuvant treatment of colon cancer. Clin Transl Oncol. 2006;8:98-102.
38. Cavanna L, Artioli F, Codignola C, Lazzaro A, Rizzi A, Gamboni A, et al. Oxaliplatin in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic gastric cancer (MGC). Am J Clin Oncol. 2006;29:371-5.
39. Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. Ann Oncol. 2006; 17:259-61.
40. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26:2006-12.
41. Rothemberg ML, Navarro M, Butts C, Bang Y, Cox JV, Goel R, et al. Phase III trial of capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2nd-line treatment for patients with metastatic colorectal cancer (MCRC). J Clin Oncol (Meeting Abstracts). 2007;25: 4031.
42. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352:2696-704.
43. Schmoll HJ, Cartwright T, Tabernero J, Nowachi MP, Figer A, Maroun J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol. 2007;25:102-9.