Review Article

Kasr El-Aini J. Clin. Oncol. Nucl. Med.
Vol. 10, NO. 1-2, 2014: 1-5

Management of Metastatic Unresectable Disease Of Colorectal Cancer Origin (Part 1: Cytotoxic Therapy)

Mohamed Abdulla

Department of Clinical Oncology, Kasr Al-Aini School of Medicine,Cairo University

Corresponding Author: Mohamed Abdulla **E-mail:** Mohamed.Abdulla@oncologyclinic.org

INTRODUCTION

Colorectal cancer is the second most common cancer in incidence and mortality in the United States with matched figures in Europe[1]. At present, the majority (75 - 80%) of colorectal cancers are diagnosed as stages I-III, in which curative surgical resection can be attempted with very good results[2]. Inspite of current efforts in improving screening programs, (20 – 25%) of patients are diagnosed with stage IV disease. This subgroup of patients has a much worse outcome, with 5-year survival of around 10%. Long term survival among patients with stage IV disease is limited to a very small proportion of patients that can undergo metastatectomy[3].

For decades, 5-fluorouracil (5-FU) was the sole active agent for metastatic colorectal cancer. This has changed markedly since the year 2000, with the approval of Irinotecan, Oxaliplatin, three humanized monoclonal antibodies that target vascular endothelial growth factor (Bevacizumab) and the epidermal growth factor receptor (Cetuximab and Panitumumab), the intravenous Aflibercept, a recombinant fusion protein capable of inhibiting VEGF receptor 1 and 2 and Regorafinib, an orally active inhibitor of angiogenic tyrosine kinases including VEGF receptors 1, 2 and 3. Patients are usually treated with 2 – 3 lines of different cytotoxic combinations in addition to biologics, where the median overall survival improved over time from 10 – 12 months to more than 24 months, however, the best way to combine and sequence these agents is not yet established[4]. The drug category, mechanism of action and FDA indication in the metastatic setting is illustrated in Table (1).

Cytotoxic Therapy: Lessons Learned Over Decades of Clinical Trials:

1. Intravenous & Oral Fluoropyrimedine:

Until the development of combination regimens of Leucovorin-modulated 5-FU with either Irinotecan or Oxaliplatin, 5-FU was the standard first line therapy for metastatic colorectal cancer and it is still used in patients who cannot tolerate these triple drug regimens. If it is to be used alone because of favorable toxicity profile, it is recommended to use short infusional 5-FU/ LV (i.e. The de Gramont regimen)[5], rather than Mayo Clinic regimen of treatment for 5 consecutive days once per month. An acceptable alternative is weekly 5-FU (500 mg/m^2) plus LV (500 mg/m^2) for six of every eight weeks cycles[6].

Oral Capecitabine is a more convenient but not necessarily less toxic alternative to LV-modulated 5-FU in clinical sittings where Fluoropyrimedine alone are indicated in patients who are not considered appropriate candidates for more intensive treatment[7].

UFT is a 4:1 molar combination of ftorafur with uracil, which competitively inhibits the degradation of 5-FU, resulting in sustained plasma and intratumoral concentrations. Response rates are approximately 25 percent with UFT monotherapyand 40 percent in combination with oral LV (150 mg daily). In phase III studies, UFT plus LV has comparable efficacy and better tolerability as compared to IV bolus 5-FU. The dose limiting toxicity is diarrhea. Myelosuppression and hand-footsyndrome are infrequent[8].

Table 1: Available Drugs for Metastatic Colorectal Cancer

Drug	Category	Mechanism of Action	FDA Indication
5-Fu	Antimetabolite (Pyrimidine Analog)	Non-competitive inhibition of thymidylate synthase	1991: palliative treatment of colon cancer
Oxaliplatin	Alkylating agent(Platinum)	Inhibits DNA synthesis by forming inter and intra strand crosslinks with DNA	2002: 2nd line with 5-FU, after irinotecan failure 2004: 1st line with 5-FU
Irinotecan	Camptothecin	Inhibits topoisomerase I, producingDNA breaks	1998: 2nd after failure of 5-FU based therapy 2000: 1st line with 5-FU/LV
Capecitabine	Antimetabolite (pyrimidine analog)	Pro-drug of 5-FU	2001: 1st line when treatment with f-pyrimidine therapy alone is preferred
Bevacizumab	Humanized monoclonal antibody	Binds to VEGF, inhibiting interaction between VEGF and its receptor	2004: 1st line with 5-FU based therapy 2006: 2nd line with 5-FU based therapy
Cetuximab	Recombinant, chimeric, monoclonal antibody	Binds to EGFR, inhibiting binding of EGF	2004: single agent or with irinotecan, onirinotecan refractory or intolerant 2009: amended only for patients with KRAS wild type
Panitumumab	Recombinant, human, monoclonal antibody	Binds to EGFR, inhibiting binding of EGF	2006: single agent on chemo-refractory. 2009: amended only for patients with KRAS lacking mutations in codon 12 and 13

Quoted from "Evolvement of the Treatment Paradigm for Metastatic Colon Cancerfrom Chemotherapy to Targeted therapy. Santiago A. and Sanjay G. Critical Reviews in Oncology/Hematology 83 (2012) 47–58"

Raltitrexed (Tomudex), a folate analog, is a pure thymidylate synthase inhibitor. It is not more active than5-FU and is not approved in the US. In at least one randomized trial that assigned 905 patients with metastatic colorectal cancer to raltitrexed,infusional 5-FU, or bolus plus short-term infusional 5-FU/LV (the de Gramont regimen), raltitrexed was associated with thegreatest toxicity and worst health-related quality of life. It may be a useful substitute for 5-FU in patients with dihydropyrimidinedehydrogenase deficiency (which markedly increases 5-FU toxicity), or possibly as a component of second-line therapy inpatients failing irinotecan or oxaliplatin[9].

2. Irinotecan& Oxaliplatin:

Irinotecan:

It is a topoisomerase I inhibitor, active as a monotherapy in advanced colorectal cancer at different dose schedules, however, it preferred to be used in combination with other cytotoxics as well as targeted agents being associated with higher activity[10]. A major issue with irinotecan is the marked inter-patient variability in pharmacodynamics and kinetics that correlates poorly with body surface area – based dosing, as kinetic variability has been related to biliary excretion, where, even modest elevations in serum bilirubin, increases the risk for severe neutropenia and diarrhea; hence, a lower starting doses is appropriate in such patients particularly those receiving weekly schedule[11].

The active form of irinotecan (SN-38) is metabolized by the polymorphic enzyme UGT1A1. Intra-tumoral enzymatic activity is reduced in individuals who inherit genetic polymorphisms such as UGT1A1*28 allele. Initial reports suggested that UGT1A1*28 homozygotes (and heterozygotes to a lesser extent) were at high risk for irinotecan related GI toxicity and neutropenia[12], where FDA in 2005 recommended a modification of drug labeling to specify such individuals and a genetic assay became available at that time. However, routine testing in all patients has not been accepted for several reasons[13]; only 10% will be identified as being homozygous, whether initial dose reduction is needed and how much to reduce the dose remain unresolved issues, and the cost – effectiveness of pharmacogenetic testing for UGT1A1 before irinotecan administration remains uncertain.

Survival gains were reported in early trials following incorporation of irinotecan into a backbone of fluoropyrimidines. In a phase III study of infusional 5-FU+/- irinotecan, the OAS improved from 14 to 17 months ($P = .031$) and 1 – year survival from 59% to 69%

with the addition of irinotecan[14]. The use of infusional 5-FU/LV and irinotecan (FOLFIRI) had demonstrated superiority over the weekly bolus irinotecan and 5-FU/LV (IFL) for PFS (7.6 / 5.9 months P = .04) but failed to do so for OS (23.1 /17.6 months P = .09), moreover, the infusional regimen had coupled with significantly better toxicity profile. Capecitabine and irinotecan and irinotecan (CapeIRI) was fraught with toxicity and had similar PFS and OS results as IFL, supporting the preferences for FOLFIRI treatment[15].

Oxaliplatin:

It is the only platinum derivative approved to date with a significant activity in metastatic colorectal cancer in combination with 5-FU[16]. Early phase II data suggested activity for oxaliplatin alone for first line therapy (20 – 25% response rate), however, subsequent randomized data (albeit for 2nd line therapy) have shown a fairly low level of activity. As a result, most clinicians consider single agent oxaliplatin to be inappropriate choice for first line therapy in metastatic colorectal cancer[17].

Oxaliplatin exerts its cytotoxic effect through formation of inter and intra-strand DNA adducts leading to inhibition of DNA replication and apoptosis. Recently, there have been a few studies examining the role of Single Nucleotide Polymorphisms in DNA repair pathways in patients receiving 5-FU/Oxaliplatin in colorectal cancer although the results have been conflicting and inconclusive[18].

On the heels of irinotecan came a treatment option with oxaliplatin in combination with 5-FU/LV (FOLFOX4). Survival was not improved for Oxaliplatin based regimen compared to 5-FU/LV (16.2 /14.7 months P = .12), although PFS significantly improved by nearly 3 months and the lack of difference was thought to be due, in part, to cross over to salvage chemotherapy[19]. Capecitabine also was combined with oxaliplatin in NO16966 trial, demonstrating non inferiority of (CapeOX) compared to (FOLFOX4) for both median OS and PFS[20].

Oxaliplatin or Irinotecan Based Combination as 1st Line Therapy?

Given the reported inferiority of (IFL) to the more widely practiced (FOLFIRI) regimen in the form of outcome and patients' compliance; 2 phase III trials were designed in a head to head comparative fashion trying to answer a specific question: to start with (FOLFOX4) or (FOLFIRI) regimen as a first line systemic therapy for advanced colorectal cancer? An earlier Italian phase III study by Colucci and colleagues reported no significant differences in RR, TTP or OS between the 2 regimens[21]. The later GERCOR study confirmed that either (FOLFOX4) or (FOLFIRI) followed by the other combination at the time of progression did not significantly influence PFS or OS[22]. A retrospective analysis of the use of all three agents(fluoropyrimidines, oxaliplatin, and irinotecan) concludedthat initial combination chemotherapy and useof all three drugs during the disease course predictedbetter outcomes than the use of fewer than threedrugs[23].

Chemotherapy Breaks or Holidays:

The OPTIMOX2 study examined treatment breaks after initial multi-agent treatment versus lower-intensity treatment. Patients randomized to "maintenance treatment," consisting of mFOLFOX7 (six cycles) followed by 5FU/LV until progression, at which time therapy was re-escalated to mFOLFOX7, had significant improvements in PFS and duration of disease control. However, there was no statistically significant survival benefit in comparison to those in which 5FU/LV was replaced by a complete break from chemotherapy (median OS 23.8 v 19.5 months, P = .42) and 2-year OS was50% and 39%, respectively .This suggested that a chemotherapy-free interval may be appropriate for certain as yet undefined patients but that patients cannot be identified prior to determination of their response[24].

The Medical Research Council COIN study also addressed the question of intermittent chemotherapy in the first-line setting. Patients were randomized to continuous chemotherapy with fluoropyrimidine / oxaliplatin versus 12 weeks of the same therapy followed by a break, with reinstitution of the same treatment at the time of progression. This trial demonstrated that using chemotherapy-free intervals in this manner was notinferior to continuous treatment, and in fact patients generally reported better toxicity profiles and quality oflife[25].

S1 plus Oxaliplatin:

S-1 is an oral fluoropyrimidine that includes three different agents: ftorafur (tegafur), gimeracil (5-chloro-2,4dihydropyridine, a potent inhibitor of DPD [dihydropyrimidine dehydrogenase]), and oteracil (potassium oxonate,which inhibits phosphorylation of intestinal 5-FU, thought responsible for treatment-related diarrhea).The combination of S-1 plus oxaliplatin (SOX) was directly compared to XELOX in a multicenterrandomized Korean phase III trial of 340 patients with previously untreated metastatic colorectal cancer. SOX was statistically noninferior to standard CAPOX in terms of PFS (HR 0.79), and demonstrated a significantly higher response rate (48 versus 36%), but more grade 3 or 4 neutropenia, thrombocytopenia, and diarrhea[26].

Oxaliplatin plus Irinotecan Combination Chemotherapy:

Regimens that contain both irinotecan and oxaliplatin are notyet a standard approach for first-line or salvage treatment after failure of an irinotecan or oxaliplatin-based regimen, and their use is not suggested outside of a clinical trial. Many published phase II and III trials indicated higher response rates but with questionable impact on OAS and definite higher toxicity profiles in the majority of them. FOLFOXIRI might be exceptionally used for conversion therapy in patients with initially unresectable liver metastases who might become candidates for surgical resection if the response to chemotherapy is sufficient, and perhaps IROX in the unusual case of a patient with severe DPD deficiency. This approach should be used cautiously in older patients[27].

Oxaliplatin – Induced – Neurotoxicity:

The major dose-limiting toxicity with oxaliplatin is neurotoxicity. There are two distinct syndromes: (a) A reversible cumulative sensory neuropathy, with distal sensory loss and dysesthesias. The incidence of grade 3 neuropathy with cumulative doses of 850 mg/m^2 is 10 to 15 percent, and rises thereafter. (b) An acute neurosensory complex, which consists of striking paresthesias and dysesthesias of the hands, feet, and perioral region, jaw tightness, and unusual pharyngo-laryngo-dysesthesias. Patients need to be warned not to drink cold fluids in the days around their oxaliplatin infusions. Lengthening the infusion duration from two to six hours can prevent recurrence of the pseudo-laryngospasm. Early data suggests that inheritance of certain polymorphisms in the drug metabolizing enzyme glutathione-S transferase gene(GSTP1-105) influences the risk of oxaliplatin-induced neurotoxicity. However, further studies are needed before routine genetic testing for GSTP1-105 genotype can be recommended as a means of selecting patients for oxaliplatin-based chemotherapy. The use of calcium gluconate and magnesium sulphate as a pre- and post-medications with oxaliplatin administration in a randomized trial failed to decrease neuropathy following FOLFOX4 regimen in adjuvant sitting[28].

CONCLUSION

In conclusion; the majority of patients with advanced un-resectable colorectal cancer cannot be cured apart from the minority deemed resectable following initial successive conversion therapy to achieve metastatectomy. Aggressive therapies are usually warranted aiming at reducing disease burden with possible positive impact on quality of life as well as optimizing survival outcome. Following decades of adopting 5-FU as a sole treatment, the introduction of irinotecan and oxaliplatin had yielded substantial gains in overall response rates and survival. No matter the drug sequencing, therapeutic gain is to be anticipated following exposure to triplets rather than duplets and the decision regarding the initial combination is the sum of physician's preferences and the anticipated complications. The use of combinations containing irinotecan and oxaliplatin with or without fluoropyrimidines should not be offered outside clinical trial setting particularly in elderly patients with possible exception if conversion therapy for unresectable organ confined disease is attempted. The decision to have treatment breaks is logic in some patients aiming at achieving better quality of life without ameliorating outcome.

REFERENCES

1. Aparo S, Goel S. Evolvement of the treatment paradigm for metastatic colon cancer. From chemotherapy to targeted therapy. Crit Rev Oncol Hematol. 2012 Jul;83(1):47-58.
2. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol. 2010 Jan 10;28(2):264-71.
3. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, *et al*. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD. 2010; Available: http://seer.cancer.gov/csr/1975 2007.
4. Saltz LB, Clarke S, Díaz Rubio E, Scheithauer W, Figer A, Wong R, *et al*. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol. 2008 Apr 20;26(12):2013-9.
5. de Gramont A, Bosset JF, Milan C, Rougier P, Bouché O, Etienne PL, *et al*. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study. J Clin Oncol. 1997 Feb;15(2):808-15.
6. Petrelli N, Herrera L, Rustum Y, Burke P, Creaven P, Stulc J, *et al*. A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol. 1987 Oct;5(10):1559-65.
7. Weingart SN, Brown E, Bach PB, Eng K, Johnson SA, Kuzel TM, *et al*. NCCN Task Force Report: Oral chemotherapy. J Natl Compr Canc Netw. 2008 Mar;6(Suppl 3):S1-S14.
8. Kopec JA, Yothers G, Ganz PA, Land SR, Cecchini RS, Wieand HS, *et al*. Quality of life in operable colon cancer patients receiving oral compared with intravenous chemotherapy: Results from National Surgical Adjuvant Breast and Bowel Project Trial C-06. J Clin Oncol. 2007 Feb 1;25(4):424-30.

9. Cortinovis D, Bajetta E, Di Bartolomeo M, Dognini G, Beretta E, Ferrario E, *et al*. Raltitrexed plus oxaliplatin in the treatment of metastatic colorectal cancer. Tumori 2004 Mar-Apr;90(2):186-91.
10. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, *et al*. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998 Oct 31;352(9138):1407-12.
11. Michael M, Thompson M, Hicks RJ, Mitchell PL, Ellis A, Milner AD, *et al*. Relationship of hepatic functional imaging to irinotecan pharmacokinetics and genetic parameters of drug elimination. J Clin Oncol. 2006 Sep 10;24(26):4228-35.
12. McLeod HL, Sargent DJ, Marsh S, Green EM, King CR, Fuchs CS, *et al*. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: Results from North American Gastrointestinal Intergroup Trial N9741. J Clin Oncol. 2010 Jul 10;28(20):3227-33.
13. Shulman K, Cohen I, Barnett Griness O, Kuten A, Gruber SB, Lejbkowicz F, *et al*. Clinical implications of UGT1A1*28 genotype testing in colorectal cancer patients. Cancer 2011 Jul 15;117(14):3156-62.
14. 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 Mar 25;355(9209):1041-7.
15. Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, *et al*. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: Results from the BICC-C Study. J Clin Oncol. 2007 Oct 20;25(30):4779-86.
16. deBraud F, Munzone E, Nolè F, De Pas T, Biffi R, Brienza S, *et al*. Synergistic activity of oxaliplatin and 5-fluorouracil in patients with metastatic colorectal cancer with progressive disease while on or after 5-fluorouracil. Am J Clin Oncol. 1998 Jun;21(3):279-83.
17. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, *et al*. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol. 2003 Jun 1;21(11):2059-69.
18. Henriette Tanja L, Guchelaar HJ, Gelderblom H. Pharmacogenetics in chemotherapy of colorectal cancer. Best Pract Res Clin Gastroenterol. 2009;23(2):257-73.
19. 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 Aug;18(16):2938-47.
20. Cassidy J, Clarke S, dı´az Rubio E, Scheithauer W, Figer A, Wong R, *et al*. Randomizedphase III study of capecitabine plus oxaliplatin comparedwith fluorouracil/ folinic acid plus oxaliplatin asfirst-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008 Apr 20;26(12):2006-12.
21. 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 Aug 1;23(22):4866-75.
22. Tournigand C, André 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 Jan 15;22(2):229-37.
23. Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. J Clin Oncol. 2005 Dec 20;23(36):9441-2.
24. Chibaudel B, Maindrault Goebel F, Lledo G, Mineur L, André T, Bennamoun M, *et al*. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol. 2009 Dec 1;27(34):5727-33.
25. Adams R, Wilson RH, Seymour MT, Meade AM, Madi A, Cassidy J, *et al*. Intermittent versus continuous oxaliplatin-fluoropyrimidine (Ox-Fp) chemotherapy (CT) in first-line treatment of patients (pts) with advanced colorectal cancer (aCRC): Predictive factors (PF), quality of life (QL) and final efficacy results from the MRC COIN trial. J Clin Oncol. 2010;15(Suppl.):abstr. No. 3525.
26. Hong YS, Park YS, Lim HY, Lee J, Kim TW, Kim KP, *et al*. S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: A randomised, non-inferiority phase 3 trial. Lancet Oncol. 2012 Nov;13(11):1125-32.
27. Sanoff HK, Sargent DJ, Campbell ME, Morton RF, Fuchs CS, Ramanathan RK, *et al*. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol. 2008 Dec 10;26(35):5721-7.
28. Ruzzo A, Graziano F, Loupakis F, Rulli E, Canestrari E, Santini D, *et al*. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol. 2007 Apr 1;25(10):1247-54.