Editorial

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

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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).

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 CancerfromChemotherapy to Targeted therapy. Santiago A. and Sanjay G. Critical Reviews in Oncology/Hematology 83 (2012) 47–58"

Cytotoxic Therapy: Lessons Learned Over Decades of Clinical Trials:

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/m2) 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].

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].

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 3neuropathy 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].

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.

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