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Evolvement of the treatment paradigm for metastatic colon cancer. From chemotherapy to targeted therapy

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Abstract

Colorectal Cancer is the second most common cancer in incidence and mortality in the United States. In spite of current screening strategies 1 out of 5 patients still presents with metastatic disease. During the last 10–15 years there has been significant increase in the availability of chemotherapy options for this disease. The recent introduction of molecular markers to the treatment algorithm allows oncologists to tailor treatments for each particular patient. In the following article we give an overview of the landmark publications that led to our current standards and we give our view on particular situations in which the available evidence is not so helpful in making therapeutic decisions.

Keywords

Colorectal Neoplasms; Neoplasm Metastasis; therapy

1. INTRODUCTION

It is estimated that approximately 143.000 men and women will be diagnosed with colorectal cancer and that 51.000 people will die of it in 2010, according the last update from the Surveillance Epidemiology and End Results (SEER) data from the National Cancer institute (NCI). At present, the majority (80%) of colorectal cancers are diagnosed as stage I to III, in which curative surgical resection can be attempted with very good results. Based on statistics from SEER database (includes only people in USA), when disease is confined to the colon only (stage I and II) the 5-year relative survival after surgery alone is 90% (58%-97%), but if it has spread to the regional lymph nodes (stage III) the 5-year relative survival drops to 70% (16%-91%) [1]. In spite of current efforts in improving screening programs, 20% of patients are diagnosed once their tumor has metastasized (stage IV disease). This subgroup of patients has a much worse outcome, with 5 year survival of

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around 10%. Long-term survival is infrequent once metastatic disease is present and is limited to a very small proportion of patients that can undergo metastasectomy [2].

Over the last 10–15 years the median overall survival for patients with metastatic colon cancer has doubled. This was accomplished mainly due to the introduction of newer chemotherapeutic drugs and regimens, including the use biologics or targeted agents. The median overall survival (OS) improved from 10–12 months in patients treated with 5-fluororuracil (5-FU)/leucovorin (LV) [3,4] to 20–21 months reported in recent clinical trials using a 3 drug combination [5].

Currently, there are 7 FDA approved drugs for the treatment of metastatic colon cancer. Typically these are used in combination. However some drugs can be given as single agents. On average, patients undergo two to three lines of treatment, making the existing therapeutic algorithm much more complex than 10 years ago. In its last update, the National Comprehensive Cancer Network (NCCN) guidelines supports 12 different drug combinations as possible options for first line treatment in patients with metastatic colon cancer [6]. Given the wide availability of these agents and the complexity of the current treatment paradigm it is of great importance to fully understand the efficacy and different toxicity profiles of these agents in order to better tailor our therapies to each individual patient.

2. AVAILABLE DRUGS

In the following section we describe basic information about the 7 drugs that are available for the treatment of metastatic colon cancer together with the results of the landmark studies that led to their approval and current indications (see Table-1).

2.1. 5-Fluorouracil

It belongs to a group of drugs called antimetabolites. It is a pyrimidine analog that works through noncompetitive inhibition of the enzyme, thymidylate synthase. It requires enzymatic conversion (ribosylation and phosphorylation) to form specific metabolites that exert its cytotoxic activity; triphosphate fluxoridine (FUTP) which is incorporated into the RNA and fluorodeoxyuridine monophosphate (FdUMP) which inhibits thymidylate synthesis, necessary for DNA replication. It is an S-phase specific drug that induces cell cycle arrest and apoptosis. In addition to being incorporated into DNA and RNA it has been shown to inhibit the activity of the exosome complex, an exoribonuclease complex of which activity is essential for cell survival.

It is administered as an intravenous bolus and/or infusion, typically every 2 weeks. Doses vary depending on the regimen and combination used. Folinic Acid (leucovorin) is typically given in conjunction with 5-fluorouracil since it enhances its cytotoxic activity by increasing the formation of ternary complexes with thymidylate synthase.

Metabolic degradation occurs mainly in the liver, by dihydropyrimidine dehydrogenase (DPD). The Food and Drug Administration (FDA) labeling does not contain formal guidelines for dose adjustment for hepatic impairment. Floyd et al recommends avoiding usage when bilirubin is ≥5 mg/dl [7]. On the other hand Koren et al recommends dose reductions of ≥ 50% in hepatic impairment, but does not specify a cutoff value [8]. We think that extreme caution should be taken in patients with total bilirubin of ≥ 5 mg/dl. Individuals who lack DPD may experience profound toxicity.

The most common adverse effects are fatigue, stomatitis, nausea, diarrhea, myelosupression, increased pigmentation and atrophy of the skin and hand-foot syndrome.

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Many studies have evaluated the role of 5-FU/LV in metastatic colon cancer, using different regimens and ways of administration. A meta-analysis published in 1998, showed that 5-FU administered as a continuous infusion (CI) was superior to 5-FU given as a bolus; with superior response rate (RR) (22% in 5-FU CI vs. 14% in 5-FU bolus, p= 0.0002) and better median OS (HR 0.88, 95% CI, 0.78 to 0.99; p= 0.04) [3]. A second meta-analysis published in 2004 that included 3338 patients showed that tumour responses doubled with the addition of LV to 5-FU regimens (RR 21% in 5-FU/LV vs. 11% in 5-FU alone; p= 0.0001). The combined survival analysis showed a survival advantage in favour of 5-FU/LV (HR of 0.90; 95% CI, 0.87 to 0.94, p= 0.004) [4]. The median OS from these two meta-analyses were 12.1 and 11.7, respectively.

In conclusion, 5-FU should be used in combination with LV and should be administered as a CI whenever possible (currently used regimens include a combination of infusional and bolus 5-FU), in order to achieve its maximum efficacy. This chemotherapy backbone of 5-FU/LV has been used as the control arm in multiple subsequent clinical trials that tested newer drug combinations.

2.2. Oxaliplatin

It is a third-generation diaminocyclohexane (DACH) platinum analog. It undergoes nonenzymatic conversion in physiologic solutions to active derivatives, including monoaquo and diaquo diaminocyclohexane platinum, which covalently bind to DNA. It kills tumor cells in all stages of the cell cycle and binds to DNA through the formation of intrastrand and interstrand cross-links, thereby leading to inhibition of DNA synthesis and function. In addition to targeting DNA, the platinum analogs have also been shown to bind to both cytoplasmic and nuclear proteins, which may also contribute to their cytotoxic and antitumor effects. It is dosed at 85–100 mg/m2 (as a 2-hour intravenous infusion) every 2 weeks or 130mg/m2 every 3 weeks. It is rapidly distributed into tissues or eliminated in the urine. It undergoes rapid and extensive nonenzymatic biotransformation. It is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. The major route of platinum elimination is renal excretion and its renal clearance is significantly correlated with the glomerular filtration rate (GFR).

The most common adverse effects are nausea, vomiting, diarrhea, fatigue and myelosupression. A major toxicity of oxaliplatin is peripheral neuropathy that may manifest in 2 different forms. The acute: reversible neuropathy is usually triggered by exposure to cold temperature. It presents as transient paresthesia, dysesthesia or hypoesthesia in the hands, feet, perioral area, and a more psychologically discomforting laryngo-pharyngeal dysesthesia, manifested by a subjective sensation of choking especially on ingesting cold liquids. The chronic: persistent, sometimes irreversible neuropathy presents as paresthesias, dysesthesias or hypoesthesias; but may also include deficits in proprioception that can interfere with daily activities (writing, walking). The chronic form is typically the dose limiting toxicity.

Oxaliplatin demonstrated to be beneficial as a component of second line therapy. A study published in 2003, randomized 463 patients who had failed first line therapy with IFL (irinotecan based regimen, considered standard of care at that time) to 5-FU/LV bolus and infusion vs. oxaliplatin alone vs. combination (FOLFOX4). FOLFOX4 arm proved to be superior with a RR of 10% vs. 0% (p= 0.0001) and a time to progression (TTP) of 4.2 months vs. 2.7 months (p= 0.001) when compared to the 5-FU/LV arm. Oxaliplatin as a single agent was no better than 5-FU/LV. Patients in the FOLFOX4 arm had more neutropenia, neutropenic fever and gastrointestinal adverse effects [9]. Therefore, oxaliplatin was considered rather inactive as a single agent, and the ideal way for its administration is in combination with 5-FU.

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As front line therapy, de Gramont et al, reported the results of a large phase III randomized trial in which patients received 5-FU/LV vs. FOLFOX4. This study showed superiority of FOLFOX4 over 5FU/LV, with a RR of 50% vs. 22% (p= 0.0001), a progression free survival (PFS) of 9 months vs. 6 months (p= 0.0003) and a median OS trend (16 months vs. 14.7 months, p= 0.12) favoring FOLFOX4. The main toxicities were diarrhea, neuropathy and neutropenia; which did not interfere with patient's quality of life as reported. However, it is important to mention that almost 70% of the patients developed neurosensory toxicity and in 18% it was at least grade 3 [10]. In 2004, 3 regimens were compared head to head as upfront treatment; IROX (irinotecan and oxaliplatin), IFL (standard of care at that time) and FOLFOX4. FOLFOX4 demonstrated to be superior in comparison to rIFL (control arm, in which IFL was modified to lower doses, due to increased toxicity) with a RR (48% vs. 32%, p= 0.006), a median PFS (8.7 months vs. 6.9 months, p= 0.0014) and a median OS (19.5 months vs. 15 months, p= 0.0001). IROX was equal to IFL [11]. Later, a smaller phase III study done in Europe comparing FOLFOX4 and FOLFIRI showed similar median OS of 15 months in the FOLFOX4 arm [12].

2.3. Irinotecan

It is a derivative of camptothecin, isolated from the tree Camptotheca acuminata. Irinotecan is an S phase specific agent and binds to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. These lesions are reversible and not toxic by themselves to the cell. However, the collision of a DNA replication fork with the cleaved strand of DNA causes an irreversible double-strand DNA break, leading to cell death. Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38, which is approximately 1000 times more potent than irinotecan as an inhibitor of topoisomerase I. However, plasma levels of irinotecan are around 10–50 times that of SN-38 and the precise contribution of SN-38 to the overall activity of irinotecan is therefore unknown. The recommended dose ranges from 50 to 350 mg/m2. It can be given every 2 weeks (typically in combination with a fluoropyrimidine); or every 1 or 3 weeks as a single agent.

The conversion of irinotecan to SN-38 is mediated by the enzyme carboxylesterase and primarily occurs in the liver. SN-38 is subsequently conjugated also in the liver by the enzyme -glucuronosyl transferase 1A1 (UGT1A1) to form the inactive metabolite SN-38 glucuronide, which is eliminated in the bile and urine. Its clearance is diminished in patients with hepatic dysfunction and in patients with an inherited deficiency in the UGT1A1 (Gilbert's syndrome). As a result, patients with these disorders are at increased risk for severe irinotecan induced toxicity. SN 38-G is in turn converted to the active SN-38 via beta-glucorinidases in the human intestine, the predominant source of which is intestinal bacteria.

The most common adverse effects are nausea, vomiting and fatigue. It has 2 dose limiting toxicities: 1- Delayed diarrhea: which is significant with all schedules of administration. It should be aggressively treated with loperamide. 2- Myelosupression: this is worse with the every 3 week schedule.

Irinotecan was initially adopted as a second line agent. A trial published in Lancet in 1998, demonstrated that irinotecan as a single agent was superior to best supportive care (BSC) in patients who had failed 5-FU based therapy. This study showed a median OS of 9.2 months vs. 6.5 months (p= 0.0001), favouring irinotecan. Patients receiving irinotecan had greater palliation of cancer related symptoms, including pain [13].

Subsequently, many different irinotecan based regimens have been proven effective as first line therapy. One of the first ones to be developed was the IFL regimen, in which irinotecan is used weekly for 4 weeks with a 2-week break; this is given in combination with bolus 5-

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FU/LV. Saltz et al demonstrated that IFL was superior to irinotecan (single agent) and to 5-FU/LV in previously untreated patients. This was demonstrated by better RR (39% vs. 21%, p= 0.001), better DFS (7 vs. 4.2, p= 0.004) and better OS (14.8 vs. 12.6, p= 0.04) for IFL over 5-FU/LV. Outcomes with irinotecan alone were similar to 5-FU/LV [14]. At the same time, the FOLFIRI regimen was developed in Europe as a first line option, in which irinotecan was used every 1 or 2 weeks in combination with infusional 5-FU/LV. This study also favoured FOLFIRI over 5-FU/LV with a RR (49% vs. 31%, p= 0.005), a median time to progression (6.7 months vs. 4.4 months, p= 0.001) and median OS (17.4 months vs. 14.1 months, p0.031) [15].

2.4. Capecitabine

Capecitabinbe (Xeloda®, Roche Inc., Nutley, NJ) is an orally administered fluoropyrimidine carbamate, a prodrug that is absorbed in the gastrointestinal tract and metabolized by a series of enzymes to the active drug 5-fluorouracil. The last enzymatic step involves thymidine phosphorylase, which is expressed in some human carcinomas in higher concentrations than surrounding normal tissues. In theory, this might be an advantage over infusional 5-FU, since the active drug will achieve higher concentrations in tumors, achieving more efficacy and less toxicity. The mechanism of action is similar to 5-fluorouracil. It is dosed at 825–1000 mg/m2 orally twice daily when used in combination with oxaliplatin or irinotecan; also dosed at 1000–1250mg/m2 orally twice daily when used as a single agent. It is typically given daily for 2 weeks at 3-week intervals. Capecitabine and its metabolites are predominantly excreted in urine.

In mild to moderate liver dysfunction due to liver metastasis the area under the curve (AUC) of capecitabine increases by 60%, so it should be used with caution in this subset of patients. There is significant interaction with warfarin and phenytoin, those usually need to have their doses reduced. The most common adverse effects are nausea, diarrhea, stomatitis and fatigue. Interestingly, capecitabine has a much higher incidence of hand foot syndrome when compared to intravenous 5-FU.

Two large trials compared the use of capecitabine as a replacement of 5-FU in combination with oxaliplatin (CapOx regimen) in front line therapy. The Spanish Cooperative Group for the Digestive Tumor Trials published a non-inferiority phase III trial comparing CapOx vs. a weekly infusional 5-FU regimen (FUOX) commonly used in Spain. The results were similar for both arms; with a RR of 37% vs. 46% (p= 0.5), a median PFS of 8.9 vs. 9.5 months (p= 0.15) and median OS of 18.1 vs. 20.8 months (p= 0.14) [16]. Cassidy et al, published a larger non-inferiority phase III trial, in which the authors tested CapOx vs. FOLFOX4 (both arms were also randomized to receive either bevacizumab or placebo). Results showed similar RR of 47% vs. 48%, a median PFS of 8 vs. 8.5 months (not statistically significant) and a median OS of 19.8 vs. 19.6 months [17]. Two other trials showed similar results when replacing 5-FU with capecitabine for patients with metastatic disease receiving 5-FU/oxaliplatin based regimens [18,19]. Throughout all these studies, patients receiving capecitabine had greater incidence of Hand-Foot Syndrome.

2.5. Bevacizumab

Bevacizumab (Avastin®, Genentech, South San Francisco, CA) is a humanized monoclonal antibody that targets the vascular-endothelial growth factor (VEGF). It binds VEGF and prevents the interaction of VEGF with its receptors (Flt-1 and KDR) on the surface of endothelial cells. VEGF is an angiogenic growth factor that regulates vascular proliferation and permeability and inhibits apoptosis of new blood vessels. VEGF expression is increased in colorectal cancer. When VEGF is targeted and bound to bevacizumab, it cannot stimulate the growth of blood vessels, thus denying tumors blood, oxygen and other nutrients needed

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for growth. It is administered as an intravenous infusion every 2 weeks. The recommended doses for metastatic colorectal cancer are 5 mg/kg when administered with bolus IFL or 10 mg/kg every 2 weeks when used with FOLFOX4. It is not indicated to use as a single agent. No dose modifications are recommended.

The most common adverse effects are asthenia, diarrhea, hypertension, headaches, stomatitis and leucopenia. Serious complications are gastrointestinal perforation, impaired wound healing, bleeding and nephritic syndrome. Because of impaired wound healing seen in animal models, bevacizumab should not be administered for at least 4 weeks prior and after surgical procedures. Wounds should be completely healed before administration [20].

It was the first biologic agent to be approved by the USFDA as a component of upfront therapy in 2004. This approval was based on data from the Hurwitz et al paper, in which 813 patients with metastatic disease were randomized to get IFL + bevacizumab (bev) vs. IFL alone. The experimental arm showed superiority with a RR of 44.8% vs. 34.8% (p= 0.004), a median PFS of 10.6 months vs. 6.2 months (p= 0.001) and a median OS of 20.3 months vs. 15.6 months (p= 0.001) [21]. In 2008, bevacizumab was added to FOLFOX4 and CapOx regimen in first line therapy. Interestingly, the RR were similar independently of the use of bevacizumab (38% in both arms). The median PFS was 9.4 vs. 8 months (p= 0.0023), the median OS did not reach statistical significance but showed a trend in favour of the bevacizumab arm (21.3 vs. 19.9 months, p= 0.077) [5]. As second line therapy, the Eastern Cooperative Oncology Group (ECOG) conducted the E3200 trial, in which patients who progressed on a fluoropyrimidine and irinotecan based therapy were randomized to either FOLFOX4 + bev, FOLFOX4 or bevacizumab alone. This trial showed RR of 22.7% vs. 8.6% vs. 3.3% (p= 0.0001) respectively. The median PFS and OS in the FOLFOX + bev group were superior to FOLFOX alone (7.3 vs. 4.7 months; 12.9 vs. 10.2 months with a p value of 0.001). Bevacizumab alone showed only modest activity [22]. The use of bevacizumab + FOLFIRI or CAPIRI is currently being evaluated in phase III trials. An interim analysis of one of these trials was presented at the ASCO meeting in 2008, showing that is a safe combination. Efficacy data is still not available [23].

2.6. Cetuximab

Cetuximab (Erbitux®, Eli Lilly, Indianapolis, IN) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). It is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions. EGFR is constitutively expressed in many human cancers including colon and rectum. Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, blocking phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of the mitogen activated protein kinase (MAP kinase) pathway leading the downstream signaling leading to cell proliferation etc. However, in cancers with a kras mutation, the MAPK pathway is constitutively activated and is independent of external ligand dependent activation. Cetuximab can also mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types.

It is dosed as an intravenous infusion at 400 mg/m2 (initial dose) followed by a weekly dose of 250mg/m2, given either as single agent or in combination with FOLFOX, FOLFIRI or irinotecan. The most common adverse effects are acneiform rash, fatigue, dyspnea, diarrhea and nausea.

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It was first approved by the USFDA in 2004 for use in patients who progressed on irinotecan based therapy. The trial that led to the approval randomized 329 patients to irinotecan + cetuximab vs. cetuximab alone. If patients had progression on cetuximab they were able to crossover to the doublet. Results showed superiority of the combination arm with RR (22.9% vs. 10.8%, p= 0.007) and median PFS (4.1 months vs. 1.5 months, p= 0.001). Median OS was similar between the two arms (8.6 months vs. 6.9 months, p= 0.48). This trial showed that cetuximab is an active agent in metastatic colorectal cancer, particularly in chemo-refractory patients (>75% of the patients had progression in 2 or more regimens) [24]. Jonker et al, also published a trial using cetuximab in chemorefractory patients whose tumors expressed EGFR by immunohistochemistry (this study was started before the KRAS mutation status data was mature). In comparison with best supportive care, patients who received cetuximab had a median OS of 6.1 vs. 4.6 months in the control group (HR of 0.77; CI, 0.64 to 0.92; p= 0.005) [25].

In 2007, results from the CRYSTAL trial were reported, in which untreated patients were randomized to FOLFIRI + cetuximab vs. FOLFIRI alone. This large phase III included 1217 patients and was positive for the addition of cetuximab, showing a significantly higher RR (46.9% vs. 38.7%, p= 0.005), a longer median PFS (8.9 vs. 8 months; p= 0.036). Median OS was not reported [26]. In the latest update of the CRYSTAL trial, patients who had wild type KRAS had significant better responses to cetuximab than patients who carried a mutation. The median OS was 23.5 months in KRAS wild-type (wt) patients vs. 16.2 in KRAS mutated (mt) patients [27]. In a subset analysis of this trial, patients with KRAS wt who received FOLFIRI + cetuximab had better RR (57.3% vs. 38.5 %; p= <0.0001), better PFS (9.6 vs. 7.6 months; HR 0.66 [0.54–0.80]) and better OS (23.5 vs. 19.5 months; HR 0.81[0.69–0.94]), when compared to patients who received FOLFIRI alone [28]. Other reports also confirmed the importance of the KRAS mutation status as a predictive marker of response to cetuximab [29–31]. The EPIC trial tested the use of cetuximab + irinotecan vs. irinotecan in patients who failed first line chemotherapy with fluoropyrimidine and oxaliplatin. Tumors had to express EGFR. The combination arm showed better RR (16.4% vs. 4.2%, p= 0.0001) and better median PFS (4 vs. 2.6 months, p= 0.0001) compared to control the control arm. There was no statistical significance for median OS (10.7 vs. 10 months, p= 0.71) [32]. Contrary to the KRAS mutation status, the levels of EGFR expression by immunohistochemistry (IHC) do not predict response to cetuximab and should not be used as a tool to decide which patients will benefit from this agent [33].

2.7. Panitumumab

Panitumumab (Vectibix®, Amgen, Thousand Oaks, CA) is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Its mechanism of action is similar to cetuximab. It is dosed as an intravenous infusion at 6mg/kg every 14 days, given as a single agent or in combination with FOLFOX or FOLFIRI. Similar to cetuximab, the most common adverse effects are skin rash, hypomagnesaemia, fatigue, nausea and diarrhea.

Panitumumab (P) was tested as single agent and in combination with different chemotherapy agents in phase II and III trials [34]. A randomized phase III trial that included 463 patients who were refractory to chemotherapy (had progressed on 2 or 3 lines of treatment) compared panitumumab single agent vs. best supportive care (BSC). On the P arm the RR was 10%, there was an improvement in PFS (HR 0.54; 95% CI, 0.44 to 0.66; p= 0.0001) but no benefit in median OS [35].

As frontline therapy, the PRIME trial demonstrated a survival benefit trend. This trial was a randomized phase III trial that tested the addition of P to the FOLFOX regimen. For patients with KRAS wt: the RR was 55% for FOLFOX + P vs. 48% for FOLFOX, the median PFS

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was 9.6 months vs. 8 months (p=0.0234) and the median OS was 23.9 months vs 19.7 months (p= 0.07), respectively. Interestingly, patient with KRAS mt had a worse median PFS when they received panitumumab (7.3 months vs. 8.8 months, p= 0.0227) [36].

In second line therapy another large phase III trial was recently published. Patients who had prior exposure to oxaliplatin and bevacizumab, were randomized to FOLFIRI + P vs. FOLFIRI alone. For KRAS wt: the RR was 35% (experimental arm) vs. 10% (control arm), the median PFS was 5.9 months vs. 3.9 months (p= 0.004). There was a trend in median overall survival but was not statistical significant (14.5 months vs. 12.5 months, p= 0.7). There was no difference between arms in KRAS mt patients [37].

3. DID WE MAKE ANY PROGRESS SINCE 5-FU ?

While initially USFDA approved in 1962, 5-FU remains one of the most important agents in the therapy of colorectal cancer, both in the curative and the palliative setting. It forms the backbone of the combination therapy with the relatively recent cytotoxics, such as oxaliplatin and irinotecan, which have played a significant role in the improvement of outcome of patients with this illness.

We can estimate that the addition of oxaliplatin to 5-FU/LV (FOLFOX regimen) added approximately 3 months to the median PFS. However, none of these trials using oxaliplatin showed a statistically significant difference in OS compared to 5-FU/LV arms, when used in the first line setting. We hypothesize that this could be explained the fact that the control arms were also likely to be exposed to irinotecan during the course of their treatment which diluted the effect between arms and also explains the fact that the OS in the controls arms are 2–3 months higher than historical numbers from prior 5-FU/LV trials. A similar trend was observed from trials using the combination of irinotecan with 5-FU (IFL, FOLFIRI regimens). These showed RR, PFS and OS that are comparable to trials using oxaliplatin containing regimens (FOLFOX); adding approximately 3 months to PFS and OS to prior standard of 5-FU-LV regimens. However, these trials, likely due to methodological issues did show a statistical significant improvement in median OS.

It is now widely accepted that 5-FU can be safely replaced by capecitabine without compromising outcomes in patients with metastatic disease that are receiving oxaliplatin based regimens. No phase III trials evaluating the combination of irinotecan with capecitabine have been published yet. A phase III trial that compared IFL (Saltz regimen) vs. CAPIRI was closed due to poor accrual and the preliminary results showed similar RR. Unfortunately, no conclusions can be done in terms of PFS or OS [38]. Other trials are currently accruing patients to answer this question.

The first biologic agent to be approved was bevacizumab. It added approximately 1–4 months to median PFS, compared to prior standard regimens, like IFL or FOLFOX/CapOx. The greatest benefit of bevacizumab was seen when added to IFL regimen (OS advantage of 4.7 months) [17], while when added to FOLFOX/CapOx in both the first and second line therapy, the benefit was more modest (OS advantage of 1.4 and 2.1 months respectively) [5,22]. It is possible that bevacizumab is not as beneficial when used with regimens using infusional 5-FU (FOLFOX) as compared to regimens using bolus 5-FU (IFL). Bevacizumab effect may be diluted by the superiority of infusional 5-FU regimens [3]. In a subset analysis of the NO16966 trial published by Saltz (updated by Cassidy at ASCO GI Symposium in 2009), the benefit of bevacizumab in median PFS was only observed in patients receiving CapOx (HR 0.77, p = 0.026), but not on patients receiving FOLFOX (HR 0.89, p = 0.189); and the effect of bevacizumab was diluted when patients receiving placebo were accounted [39]. Ironically, in spite of no strong survival benefit evidence supporting the addition of

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bevacizumab to FOLFOX in the first line setting, this combination continues to be the favourite one and is chosen by 64% of US oncologists as the frontline regimen [40].

Subsequently, the addition of cetuximab showed significant improvement in RR. However, significant benefits in OS were seen exclusively in patients with KRAS wt status. Based on these reports, ASCO now recommends that anti-EGFR therapy in metastatic colon cancer (either with cetuximab or panitumumab) be used only for patients who lack a KRAS mutation in codon 12 nor 13 [41]. Similarly, the USFDA also recommends the use of these drugs only in patients whose tumors are wt in the kras oncogene. Similar to cetuximab, panitumumab improved survival when added to a first line regimen. However, it is still a topic of debate if these agents should be used upfront or on subsequent lines of therapy in patients with KRAS wt.

Maintenance therapy with a biologic agent beyond first progression has been suggested based on data from the Brite cohort study. In a multivariate analysis, adjusting for important prognostic factors like performance status this study showed that patients who continued chemotherapy + bevacizumab after first progression had a statistically significant better survival beyond first progression (SBP) when compared to patients who continue chemotherapy alone (19.2 months vs. 9.5 months) [42]. We think that a randomized trial needs to be done in order to formally recommend this type of approach, cohort studies are subject to potential biases.

4. WHICH REGIMEN SHOULD WE USE FIRST ?

Patients with metastatic colorectal cancer are a very heterogeneous group. The selection of the most suitable combination of drugs should be done on an individual basis, taking into account: performance status, comorbidities, organ dysfunction, toxicity profile of the regimen and how this will impact on each particular person.

Before the introduction of biologic agents, the two regimens of choice for good performance status patients as first line therapy were FOLFOX and FOLFIRI. Now, there is enough data suggesting that these regimens are equivalent when used as first line therapy. An Italian group did a phase III trial in which FOLFIRI and FOLFOX4 were compared head to head. This trial showed no difference between arms in terms of RR, PFS or OS. Toxicity profiles were different showing more gastrointestinal toxicities in the FOLFIRI arm and more myelosuppression and neurological toxicity in the FOLFOX4 arm. The GERCOR study showed that the sequence in which FOLFIRI and FOLFOX are given (first line, second line or vice versa) does not impact on PFS or OS. However, this study also emphasizes the importance of the toxicity profile when choosing a regimen. Patients who were treated with FOLFOX upfront had a median of 12 cycles. Oxaliplatin had to be stopped in a number of patients due to neurotoxicity (neuropathy) before tumour resistance developed [43]. In order to overcome this difficulty the same group published OPTIMOX 1 and 2 studies, in which the concept of stopping oxaliplatin after a certain number of cycles was introduced in order to prevent neurotoxicity. It is clear from these 2 trials that the complete cessation of chemotherapy is detrimental for patients. However, it appears to be a safe option to stop oxaliplatin after 6 cycles without compromising efficacy [44,45]. We think that these results should be interpreted with caution and the decision to stop oxaliplatin after 6 cycles should not be the standard of care; the decision should be done on an individual basis, according to the toxicities developed.

Oxaliplatin based therapy (FOLFOX) is the favourite among American physicians as the first line strategy (87% of cases), as shown by Zafar et al. He also showed that bevacizumab is the main biologic agent used as part of an upfront chemotherapy regimen (64%). The use of irinotecan increased on subsequent lines of treatment [40]. The lack of survival advantage

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of bevacizumab when added to optimal regimens like FOLFOX or CapOx suggests that the benefit of this biologic might not be as significant as we hoped or expected.

Based on current data we think that FOLFOX / CapOx +/− bevacizumab or FOLFIRI are totally appropriate and equivalent first line regimens for patients with good performance status, independent of their KRAS mutation status. For patients who are known to have KRAS wt upfront, the two approved EGFR-inhibitors should be considered as part of the upfront regimens. FOLFIRI + cetuximab or FOLFOX + panitumumab are appropriate in this setting. So far there is no upfront phase III data using the combination of FOLFIRI + panitumumab or FOLFOX + cetuximab.

There are two common situations in which we think that an oxaliplatin based regimen might not be ideal as a first option. The first situation is in patients with significant underlying peripheral neuropathy in which oxaliplatin's full potential might not be reachable due to more rapid development of dose limiting neurotoxicity. In this subgroup of patients, we think that FOLFIRI is a better option as first line treatment, with the option of adding cetuximab in the KRAS wt population. This strategy of adding cetuximab is based on results from the CRYSTAL trial and requires KRAS mutation analysis testing done upfront. The second situation is in patients in which the use of bevacizumab is of concern due to the presence of underlying comorbid factors (uncontrolled hypertension, recent cardiovascular events, and wound healing issues) that might increase the chances of severe toxicities to the drug. In this context EGFR-inhibitors may be added to first line regimens in patients with KRAS wt (FOLFIRI + cetuximab or FOLFOX + panitumumab); taking into account the different toxicity profiles that these 2 regimens have.

5. CURATIVE INTENT

A select group of patients with metastatic disease to the liver can achieve long-term survival. If metastasectomy can be performed the 5-year survival for this subgroup is about 30% as shown in one of the largest series published by Nordlinger [46]. Many different strategies have been attempted in order to improve outcomes in resectable patients and to downsize hepatic lesions that are found to be unresectable upfront. Hepatic arterial infusion with fluroxidine after hepatic resection showed decrease in liver recurrences but failed to demonstrate improvement in survival at 4-years when compared to no intervention ($p= 0.6$) [47,48]. Surprisingly, there is only one phase III trial evaluating the role of perioperative chemotherapy in patients with resectable liver metastasis. This trial randomized patients to FOLFOX for 6 cycles (pre and postoperative) vs. surgery alone. The number of resections was similar in both groups. The overall RR to preoperative FOLFOX was 43% and the there was an absolute increase in PFS of 7.3% at 3 years in the experimental arm ($p= 0.58$), which did not reach statistical significance. No survival was reported [49]. Other smaller phase II trials evaluated the different combinations of neoadjuvant chemotherapy [50,51]. None of these different strategies demonstrated to improve overall survival when compared to metastasectomy alone. The best perioperative strategy should be decided on an individual basis, taking into account liver toxicity of chemotherapeutics, performance status, and burden of liver disease.

A different group of patients are those who present with "liver only" metastasis that are unresectable upfront. It is our opinion, that the algorithm for these patients should be different since the goal is to "convert" them to resectability, and an attempt at curative resection. In these cases the RR of the chemotherapy regimen chosen is of extreme importance and the regimen with the higher RR for a particular case should be chosen. The highest RR ever reported on a phase III trial is 66%, from the GONO trial using FOLFOXIRI [52]. A subgroup analysis of this trial showed that 20% of the patients that

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were deemed unresectable before chemotherapy were able to undergo R0 liver metastasectomies [53].

In terms of the biologics to be chosen; bevacizumab showed improvement in median PFS when used as part of FOLFOX or CapOx regimens but was not accompanied with higher RR [5]. Panitumumab also failed to show higher response rates when used as a part of FOLFOX4 regimen [36]. On the other hand, when cetuximab was added to FOLFIRI demonstrated a statistical significant improvement in RR in KRAS wt patients [26]. This finding suggests that the synergistic effect of cetuximab with irinotecan seen in preclinical models may translate clinically into higher RR [54]. We think that this data justifies checking the KRAS mutation status for this subgroup of patients before deciding on the chemotherapy regimen, if the decision is to include a biologic. This is of particular importance in patients who have larger liver metastasis and rely on response rates in order to become resectable. We believe that FOLFIRI + C can be used in this subgroup, as long as no more than 6–8 cycles are administered and obese people are excluded. This is based on the increased risk of steatohepatitis with subsequent postoperative complications found when irinotecan based regimens are used prior liver metastasectomies [55,56]. There is currently an NASBP study studying the rate of conversion from nonresectable to resectable liver metastasis using FOLFOX + cetuximab in patients with tumors with KRAS wt [57].

6. FUTURE STRATEGIES

It is clear that over the last 2 decades there has been significant progress in the treatment of metastatic colon cancer with an almost doubling of the median OS (see Table-2). Better understanding of the tumor biology and molecular pathway and mechanisms of tumorigenesis has led to the discovery of novel agents with improved outcomes. We now understand that colorectal cancer is a heterogeneous disease and not all the patients should be treated the same way. The perfect example is the KRAS mutation status, wherein the patients with a KRAS mutant tumor do not benefit from EGFR inhibitors {28,29]. There is currently an urgent unmet need for new drug development and understanding of resistance mechanisms for this subgroup, since this population tend to get to this stage of disease with good performance status. Currently, only 2 phase II clinical trials are open for this population on clinical trials.gov. One is testing lenalidomide in combination with cetuximab [58] and the other is testing the immunomodulating agent Imprime PGG also in combination with cetuximab [59]. A phase I trial is also a good option for these patients if performance status allows. An exciting potential drug for this group of patients is “Reolysin”, a live formulation of reovirus, an RNA virus that has demonstrated selective replication in KRAS mutant cancer cells [60]. While this drug has entered phase III trials in head and neck cancer, its potential as an agent for KRAS mutant colorectal cancer is beginning to be investigated.

7. CONCLUSIONS

Over the last 10–15 years the treatment paradigm for metastatic colorectal cancer changed dramatically. While clinicians manipulated, played and toyed with one single drug, 5-FU for four decades, there have been 6 drugs approved by the USFDA between 1996 and 2004. Fortunately, this was translated in a significant prolongation in the median survival that went from 10–12 months to 20–23 months. These advances in drug development also taught us that not every drug is beneficial to all patients. The introduction of KRAS mutation testing in our decision tree helps us identify patients that will respond differently to therapy with EGFR inhibitors. More clinical trials are needed, particularly in KRAS mutated patients. This subgroup of patients do not benefit from EGFR inhibition, so their treatment alternatives are more limited.

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Besides great efforts in clinical research, there were no new drugs approved over the last 6 years for patients with metastatic colon cancer. We think that the identification of markers of response early on in drug development will be a fundamental step in obtaining positive results in larger phase III clinical trials. An example of this approach is the ALK and MET/HGF inhibitor (crizotinib) that showed an overall response rate of 58% in pre-treated patients with ALK rearranged non-small cell lung cancer [61]. As more targeted agents become available and tumour biology is better understood, this approach will be essential in identifying groups of patients that will benefit from these new agents. We strongly believe that at end of the day this strategy will help us make more efficient use of our resources and eventually translate into better outcomes for our patients.

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Completed his medical education at Universidad del Salvador, in Buenos Aires, Argentina. After graduating, he moved to USA for further training. He completed a residency in Internal Medicine at Jacobi Medical Center/Albert Einstein College of Medicine (Bronx, New York). He also completed a fellowship in Hematology/Oncology at Montefiore Medical Center/Albert Einstein College of Medicine.(Bronx, New York). He recently joined as junior faculty in the Department of Medical Oncology at Montefiore Medical Center. He currently holds the positiion of Assistant Professor of Medicine at Albert Einstein College of Medicine. His clinical activities and research interests are focused in gastrointestinal oncology and the development of early phase clinical trials. He is currently attending a Masters Program (M.S.) in Clinical Research Methodology at Albert Einstein College of Medicine. He is currentlly a fellow of the Bronx CREED (Center to Reduce and Eliminate Ethnic and Racial dispartities) Faculty Development Fellowship Program at Albert Einstein College of Medicine; from which he was awarded a grant to develop a Project in hispanic patients who suffer from Hepatocellular Carcinoma.

Sanjay Goel:

Completed his medical education at the Christian Medical College, in Vellore, India. He then moved to the US and completed a residency in internal medicine at the State University of New York at Brooklyn, New York. He began a fellowship in hematology and oncology at the University of Colorado at Denver, and then transferred and completed it at Montefiore Medical Center, Albert Einstein College of Medicine in Bronx, New York. He also completed a 2 year program obtaining a Master of Science (M.S.) degree in Clinical Research from the Albert Einstein College of Medicine. Soon after graduating from his fellowship he joined as a faculty in the Department of Medical Oncology at Montefiore Medical Center. He has risen through the ranks to the position of Associate Professor of Medicine. Dr. Goel has an interest in drug development of anti-cancer agents, and development of biomarkers of drug response. He has extensive experience in carrying out early phase clinical trials in collaboration with industry and the NCI, and has a number of investigator initiated clinical trials to his credit. He is currently engaged in cancer clinical trials, in phase I, and in phase II and III trials in gastrointestinal and genitourinary malignancies. He runs a research laboratory with a focus on drug and biomarker development for patients with colorectal cancer. He has presented his findings at national and international meetings and has published in a wide variety of journals. Dr. Goel is the author of over 25 original articles and a number of review papers. He currently serves as the leader of the Phase I program at the Albert Einstein Cancer Center, and the medical director of the East Campus of Montefiore Medical Center for clinical activities. He has a great interest in teaching and has been awarded with the “Best teaching faculty” award in Medical Oncology. Furthermore, he has mentored a number of fellows and residents in clinical and laboratory research. He has been awarded with the Advanced Clinical Research Award

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(ACRA) in colorectal cancer from the American Society of Clinical Oncology (ASCO) Cancer Foundation.

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Table 1

Available drugs for the treatment of metastatic colon cancer

Drug	Category	Mechanism of action	FDA indication (metastatic disease)
5-FU/LV	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, producing DNA breaks	**1998:** 2nd after failure of 5-FU based therapy **2000:** 1st line with 5-FU/LV
Capecitabine	Antimetabolite (pyrimidine analog)	Prodrug of 5-FU	**2001:** 1st line when treatment with fluoropyrimidine 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, on irinotecan refractory or intolerant **2009:** amended only for patients with KRAS lacking mutations in codon 12 and 13
Panitumumab	Recombinant, human, monoclonal antibody	Binds to EGFR, inhibiting binding of EGF	**2006:** single agent on chemorefractory **2009:** amended only for patients with KRAS lacking mutations in codon 12 and 13

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Table 2

Evolution of first line chemotherapy regimens in metastatic colon cancer

Author	Type of study	Regimen	Nº of patients	RR % (response rates)	Overall Survival (months)
5-FU-LV					
The Meta-Analysis group [4]	meta-analysis	5-FU-LV	3300 (19 trials)	21	11.7
The Meta-analysis group [3]	meta-analysis	5-FU CI	1219 (6 trials)	22	12.1
Introduction of oxaliplatin and irinotecan					
Saltz et al [14]	phase III	IFL	683	39	14
De Gramont et al [10]	phase III	FOLFOX4	420	50.7	16.2
Douillard et al [15]	phase III	FOLFIRI	387	49	17.4
Introduction of biologics					
Saltz et al [5]	phase III	CapOx / FOLFOX4 + bev	1401	38	21.3
Hurwitz et al [21]	phase III	IFL + bev	813	44.8	20.3
Van Cutsem et al [26–27]	phase III	FOLFIRI + C	1217	57.3 (kras wt)	23.5 (kras wt)
Douillard et al [35]	phase III	FOLFOX4 + P	1183	55 (kras wt)	23.9 (kras wt)

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