Review Article

Biologics in bowel cancer

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Abstract: Colorectal cancer is the third most common cancer in the United States and second leading cause of cancer death with over 50,000 patients expected to die from their disease in 2017. For patients who present at diagnosis with advanced disease the standard treatment is systemic chemotherapy. Over the last decade a number of biologic therapies have emerged as viable treatment options for advance colorectal cancer. When these new drugs are combined with chemotherapy survival is prolonged, often without a detriment to quality of life. In this chapter we will review the most active biologic options for treatment of colorectal cancer and place them in the context of a rapidly growing field.

Keywords: Colorectal cancer; biologics; immunotherapy

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Introduction

Colorectal cancer is the third most common cancer in the United States, in 2016 it is estimated that greater than 140,000 patients will be diagnosed (1). Colorectal cancer trails only lung cancer with respect to cancer mortality in the United States, over 50,000 patients are expected to succumb to their disease in 2016. Common risk factors for colon cancer include use of tobacco, inflammatory bowel disease, heavy consumption of red and processed meats, diabetes and obesity (2). About 5–10% of patients develop disease that is directly attributed to an inherited genetic syndrome. Screening in the form of colonoscopy is recommended for individuals over the age of 50 as a means of early detection for potential removal premalignant lesions. For patients who present with early stage disease, curative surgical resection is the recommended treatment. However, approximately 20% of patients present with metastatic disease in which case palliative systemic chemotherapy is the only treatment option. The spread of colorectal cancer can occur via lymphatic or hematogenous dissemination or by contiguous routes. The most common site of hematogenous dissemination is the liver, followed by the lungs and bone. Fortunately, the number of chemotherapeutic options continues to increase, from only 5-flurouracil (5-FU) 30 years ago to now more than ten FDA approved systemic agents. In this review will discuss systemic treatment options for colorectal cancer with a particular focus on emerging biologic therapy. In the era of precision medicine and targeted therapy, the current research focus centers around development of treatment specific to a patient's particular genetic tumor subtype. In this regard toxicity is minimized and efficacy maximized providing the highest level of patient care. As the field of oncology moves forward one could hope that role cytotoxic chemotherapy would become obsolete.

Systemic treatment

The standard first line treatment for patients with metastatic colorectal cancer is systemic chemotherapy, which is administered with the intent to palliative symptoms and prolong survival. Initial therapy is comprised of a cytotoxic "chemotherapeutic backbone" of 5-FU plus leucovorin or capecitabine in combination with oxaliplatin or irinotecan in addition to a biologic agent. 5-FU is a prodrug that requires multiple enzymatic steps prior to its conversion into the active phosphorylated form (3). The key metabolite, 5-fluorodeoxyuridylate monophosphate is a competitive inhibitor of thymidylate synthase, thus inhibiting DNA

synthesis (3). Leucovorin is a reduced folic acid that potentiates the effect of 5-FU. Capecitabine is a 5-FU prodrug that is administered orally and undergoes a three activation process once absorbed in the gastrointestinal tract (4). Irinotecan exerts its affects by inhibiting topoisomerase 1 resulting in DNA strand breaks, and oxaliplatin is a third generation platinum that forms covalent DNA adducts involving the complexed platinum atom (5,6).

The role of 5-FU as an active agent in advanced colon cancer is longstanding dating back several decades (7). Subsequent trials in the 1980–1990's established the advantage of adding Leucovorin to 5-FU with increase in response rate from 11% to 23%. A lack of overall survival was not demonstrated however, this may be a direct result of cross-over design in many studies (8). Following 5-FU/leucovorin, irinotecan was developed as an active agent in colon cancer, two randomized trials led to the FDA approval of irinotecan in 1996. In one study nearly 300 patients were randomized to irinotecan versus best supportive care, the treatment group was found to have an increase in 1-year survival (36% *vs.* 14%, P=0.0001) (9). A second trial randomized 267 refractory patients to either irinotecan or 5-FU, 1-year survival in the irinotecan group was increased from (32% to 45%, P=0.035) (10). The combination of FOLFIRI was established in a randomized trial of 683 patients assigned to treatment with Irinotecan combined with 5-FU and leucovorin, 5-FU and leucovorin alone or Irinotecan alone. The combination was superior to both 5-FU/leucovorin and single agent Irinotecan with response rates of (50% *vs.* 28% *vs.* 29%, P<0.001), progression free survival (PFS) (7.0 *vs.* 4.3 *vs.* 4.2 months, P=0.004) and overall survival (OS) (14.8 *vs.* 12.6 *vs.* 12 months, P=0.04) (11). Oxaliplatin was also combined with 5-FU and demonstrated a superior efficacy to 5-FU alone. In a randomized trial 420 chemo naïve patients were treated with 5-FU and Leucovorin with or without oxaliplatin, the combination group had a superior response rate (51% *vs.* 22%, P=0.0001), PFS (9.0 *vs.* 6.2 months, P=0.0003) and a trend toward increased survival (16.2 *vs.* 14.7 months, P=0.12). The OS trend was likely not significant due to cross over from 5-FU to oxaliplatin after progression.

Once FOLFOX and FOLFIRI were established as the most active combinations in colon cancer the question of the most appropriate sequencing of treatment arose. In 2004 a randomized clinical trial compared 5-FU and oxaliplatin (FOLFOX) to 5-FU and irinotecan (FOLFIRI) in the first line setting to determine the ideal initial chemotherapeutic backbone (12). At the time of progression 220 patients were randomized to the opposite regimen. There was no statistically significant difference in either median PFS or OS between the two groups. First line FOLFOX resulted in a PFS of 8.0 months (95% CI, 6.2–9.4) and first line FOLFIRI 8.5 months (95% CI, 7.0–9.5). The median OS with FOLFOX was 20.6 months (95% CI, 17.7–24.6) and with FOLFIRI 21.5 months (95% CI, 16.9–25.2, P=0.99) Based on this data it is reasonable to use either FOLFOX or FOLFIRI as the initial backbone per recommendation of the treating oncologist. The decision of one combination over the other is often based on the side effect profile. Oxaliplatin is associated with neuropathy, thus should be used in caution in patients with uncontrolled diabetes for pre-existing neuropathy. Irinotecan is associated with a higher incidence of diarrhea and alopecia, important determinants in quality of life.

EFGR inhibition

The MAP kinase pathway plays a key role in the progression of colorectal cancer. Activating mutations in KRAS result in constitutive activation of the MAP kinase pathway leading to increased cell growth (13). The most common KRAS mutations are found in exon 2, in 2009 ASCO recommended that treatment with anti-EGFR agents be restricted to the KRAS wild type population (14). Even more recent data has evolved indicating that resistance to anti-EGFR therapy can also be mediated by less common mutations in KRAS and NRAS (15). The latest ASCO clinical opinion recommends testing for these "extended RAS" mutations and recommends against the use of anti-EGFR therapy in patients whose tumor harbor these mutations (16).

There are currently two EGFR inhibitors approved by the FDA, cetuximab and panitumumab. Cetuximab is a chimeric (mouse/human) monoclonal antibody, whereas panitumumab is a fully humanized monoclonal antibody which may explain the lower rate of infusion reactions seen with panitumumab. In the landmark CRYSTAL study, chemotherapy naïve patients were randomly assigned to FOLFIRI with or without cetuximab (17). In the KRAS WT population (codon 12 and 13) response rates were significantly higher in cetuximab arm (57% *vs.* 40%, P=0.001). With regards to OS, cetuximab was also associated with an increase in OS (23.5 *vs.* 20 months, P=0.0093). Cetuximab was evaluated in the second line; patients who progressed on oxaliplatin were randomly assigned to irinotecan with or without cetuximab (18). The

cetuximab arm was associated with an increase in response rate (16.4% *vs.* 4.2%, P<0.0001), PFS (4.0 *vs.* 2.6 months, P=0.0001) but OS was not statistically significant (10.7 *vs.* 10 months, P=0.71).

The second EGFR inhibitor, panitumumab was studied in the PRIME trial in combination with FOLFOX (19). Patients in the extended RAS WT population (no mutations in exon 2, 3, and 4 of KRAS and NRAS) were found to have a significant increase in OS (HR =0.77; 95% CI, 0.64–0.94; P=0.009). However, in the historic WT RAS population (without mutations in exons 2 but with mutations in other exons or in NRAS) there was no benefit to the addition of panitumumab. Based on this data it is recommended that all metastatic patients receive extended RAS testing. Panitumumab has also been studied in combination therapy in patients with progressing disease. In a randomized phase III trial the addition of panitumumab to FOLFIRI was associated with a significant improvement compared to FOLFIRI (HR =0.73; 95% CI, 0.59–0.90; P=0.004) (20). The median PFS with the combination of panitumumab plus FOLFIRI was 5.9 *vs.* only 3.9 months with FOLFIRI. There was a nonsignificant trend towards increased OS 14.5 *vs.* 12.5 months (HR =0.85; 95% CI, 0.70–1.04; P=0.12). Of note, dual antibody treatment has been investigated and associated with worsened survival, thus is not recommended (21).

Small molecule EGFR inhibitors including erlotinib have been studied in colorectal cancer, however results were modest with limited rationale for larger studies (22).

Anti-vascular endothelial growth factors (VEGF) therapy

Angiogenesis is regulated primarily by interactions between VEGFs and VEGF receptors (VEGFRs) and play a critical role in cancer growth and metastasis. VEGF-A is the key regulator of tumor angiogenesis, endothelial proliferation, permeability, and survival. VEGF-A binds with high affinity to two structurally similar tyrosine kinase receptors, VEGFR-1 and VEGFR-2 which are both expressed on tumor vasculature. Bevacizumab is a humanized monoclonal antibody against VEGF that acts as an inhibitor of angiogenesis, in addition to increasing chemotherapy deliver to tissue by altering tumor vasculature and decreasing the elevated interstitial pressure in the tumor.

Hurwitz and colleagues conducted a study randomizing 813 patients who were previously untreated to receive irinotecan, bolus fluorouracil, and leucovorin plus bevacizumab versus irinotecan, bolus fluorouracil and leucovorin plus placebo (23). The median OS was 20.3 months in the bevacizumab arm *vs.* 15.6 months in the placebo arm, (HR =0.66; P<0.001). In a second phase III trial Saltz and colleagues evaluated 1,401 patients who were assigned in a 2×2 factorial design to capecitabine plus oxaliplatin *vs.* fluorouracil/folinic acid plus oxaliplatin, and then randomized to bevacizumab versus placebo (24). The median PFS was 9.4 months in the bevacizumab group *vs.* 8 months in the placebo group (HR =0.83; 95% CI, 0.72–0.95; P=0.0023). The median OS was 21.3 months in the bevacizumab arm *vs.* 19.9 months in the placebo group (HR =0.89; 95% CI, 0.76–1.03; P=0.77).

Ramucirumab is a fully humanized immunoglobulin monoclonal antibody that binds with high affinity to the extracellular VEGF-binding domain of VEGFR-2, thereby blocking VEGF ligands from binding this site and activating the receptor. In preclinical studies animal models treated with ramucirumab demonstrated significant antitumor activity with acceptable toxicity. In the first phase I trial including patients with refractory solid tumors three out of six colorectal patients had stable disease, two of which were durable for >30 weeks (25). In a subsequent phase II trial, 48 chemo naive patients were treated with FOLFOX and ramucirumab (26). The median PFS was 11.5 months (95% CI, 9–13 months) with objective response rate of 67% (95% CI, 52–80%) and 1-year OS was 85% (95% CI, 72–93%). In the first randomized phase III trial, (RAISE) 1,072 patients were randomized to second line FOLFIRI plus placebo *vs.* FOLFIRI plus ramucirumab (27). Of note all patients had disease that progressed after treatment with FOLFOX and bevacizumab in the first line. The median OS was 11.7 months (95% CI, 10.8–12.7 months) for the placebo group *vs.* 13.3 months (95% CI, 12.4–14.5 months). Significant grade 3 or worse adverse events in the treatment group included neutropenia (38%) and hypertension (11%). Based on this trial ramucirumab was approved in 2015 for second line use in colorectal patients whose disease has progressed during on or after therapy with bevacizumab and FOLFOX.

Aflibercept is a recombinant protein consisting of domain 2 from VEGFR-1 fused to domain 3 from VEGFR-2, attached to the hinge region of the Fc domain of human immunoglobulin. Aflibercept is a circulating antagonist that prevents VEGF receptor binding and in preclinical studies compared favorably to other VEGF inhibitors. In a phase 1 study published in 2010, 47 patients with refractory solid tumors were treated with aflibercept, dose limiting toxicities at the highest doses were rectal ulceration and proteinuria (28). In the phase II experience 236 patients were randomized

to receive first line FOLFOX plus Aflibercept 4 mg/kg or FOLFOX alone (29). The median PFS in combination group was 8.48 months (95% CI, 7.89–9.92) and 8.77 months (95% CI, 7.62–9.27) in the FOLFOX alone group. Although no difference in PFS was noted with FOLFOX plus Aflibercept in the first line a phase III trial with FOLFIRI in the second line was designed. In this study, 1,226 patients who were previously treated with oxaliplatin containing regimens were randomized to FOLFIRI plus aflibercept versus FOLFIRI plus placebo. The median OS in the combination arm was 13.5 *vs.* 12.06 months in the placebo arm (HR =0.817; 95% CI, 0.713–0.937; P=0.0032). The only notable differences in adverse events were anti-vascular endothelial effects. Based on this trial, aflibercept was approved for use in the second line with FOLFIRI following progression with an oxaliplatin containing regimen.

Finally, regorafenib is a multi-kinase inhibitor (anti-VEGF, KIT RET and BRAF) that is approved in the third line and beyond. In the CORRECT published in 2013, patient who had progressed on a least two lines of therapy were randomized to regorafenib *vs.* placebo (30). Patients treated with regorafenib had a small but statically significant increase in PFS 1.9 *vs.* 1.7 months (HR =0.49; 95% CI, 0.42–0.58) and OS 6.4 *vs.* 5 months (HR =0.77; 95% CI, 0.64–0.94). The FDA approved dose of regorafenib is 160 mg once daily, however a critical trial is currently enrolling (NCT02368886) evaluating the efficacy of the lower dose of regorafenib.

Third line

The most recent FDA approved agent for colorectal cancer is an oral combination (trifluridine and tipiracil) indicated for patients who progressed on multiple lines of therapy. Trifluridine is a thymidine-based nucleic acid analogue and tipiracil is a thymidine phosphorylase inhibitor. This compound was compared to placebo in patients who progressed on FOFLOX, FOLIRI and in some cases regorafenib. For the treatment group there was a statistically significant increase in PFS 2.0 *vs.* 1.7 months (95% CI, 0.41–0.57; P<0.001) and OS 7.1 *vs.* 5.3 months (HR =0.68; 95% CI, 0.58–0.81) (31).

Optimal first line biologic agent

The question of the ideal first line combination in KRAS WT patients remains unanswered. Two recent large trials attempted to address this specific clinical dilemma but produced conflicting results. The first trial, FIRE-3, compared first line FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in patients with KRAS exon 2 wild-type metastatic colorectal cancer (32). In the final RAS wild type population of 342 patients, the median OS was improved in the FOLFIRI plus cetuximab group compared to FOLFIRI plus bevacizumab [33.1 months (95% CI, 24.5–39.4) *vs.* 25.6 months (95% CI, 22.7–28.6); HR =0.70; P=0.011]. Interestingly there was no statistical difference in median PFS [10.4 months (95% CI, 9.5–12.2) *vs.* 10.2 months (95% CI, 9.3–11.5); P=0.77]. The fact that FIRE-3 showed a significant benefit in OS without a benefit in PFS is curious, notably this has not been a reported finding in dozens of previous colorectal clinical trials.

The second trial, CALGB/SWOG 80405 compared chemotherapy (FOLFOX or FOLFIRI) combined with cetuximab or bevacizumab in patients who were KRAS WT (codon 12 and 13) (33). In the 2,334 who were KRAS WT, OS in the chemo/bevacizumab *vs.* chemo/cetuximab groups was 29.04 months (95% CI, 25.66–31.21) *vs.* 29.93 months (95% CI, 27.56–31.21).

One potential explanation to explain the difference in these two trials is the potential varying use of second line chemotherapeutic agents (34). The FIRE-3 protocol listed recommendations for second line treatment with FOLFOX plus bevacizumab after progression on cetuximab or irinotecan plus cetuximab after progression on bevacizumab. Exact details on actual treatment are lacking, approximately one third of patients in the cetuximab group received the recommended second line treatment versus approximately only one fifth in the bevacizumab group. A second potential explanation is the use of second line bevacizumab after progression in the bevacizumab arm. In the United States it was common practice to continue anti-VEGF therapy based on data from the Bevacizumab regimens investigation of treatment effects and safety (BRITE). The OS of patients on the bevacizumab arm of FIRE-3 does is an outlier compared to multiple trials including CALGB/SWOG 80405. Examples including the Triplet Plus Bevacizumab (TRIBE) study where survival was 33.5 months (35) and the Bevacizumab, Irinotecan, Colorectal cancer-celecoxib (BICC-C) documenting a median survival of 28 months (36).

Location of primary tumor (right *vs.* left)

There is emerging data from recent trials that primary tumor location may be prognostic. The primary tumor

location was determined by chart review, 1,137 patients were KRAS wild type (codon 12 and 13) in the main cohort, 252 KRAS mutant patients were treated prior to the protocol amendment (37). Right sided was defined as cecum to hepatic flexure, left sided as splenic flexure to rectum and transverse hepatic to splenic flexure. In the KRAS wild type population, 280 patients were defined as right sided, 689 as left sided. Results were notable for a significant survival difference even after adjustments for age, gender, and prior therapy. Treatment with cetuximab based treatment was associated with increased survival compared to bevacizumab for left sided tumor (P=0.04) and bevacizumab superior to cetuximab based treatment for right sided tumors (P=0.03). For the KRAS wild type population, survival for left sided primary was 37.5 *vs.* 32.1 months for cetuximab and bevacizumab respectively and for right sided tumors 24.5 *vs.* 16.4 months favoring bevacizumab *vs.* cetuximab based treatment. It is not clear why, but clearly tumors arising in the right are distinct from those arising in the left.

Disease of the small intestine

Malignancies of the small intestine are relatively rare, incidence in United States is estimated to be approximately 10,000 in 2017 (1). Adenocarcinoma is the second most common histology, approximately 30%, trailing only neuroendocrine tumors (38). Unfortunately, patients with adenocarcinoma of the small intestine are often excluded from clinical trials, thus data on these subjects is lacking. Historically, data from patients with primary cancer of the colon is extrapolated to those patients with primary small bowel cancer. As such patients with advanced or metastatic adenocarcinoma of the small intestine are treated with biologic agents including anti-VEGF or snit-EGFR agent. It should be noted that patient's with adenocarcinoma of the small intestine are often found to have higher rates of microsatellite instability. As such the role of immunotherapy may be even more pertinent for this patient population.

Immunotherapy

A research area of rapid growth and development is that surrounding the programmed death (PD-1) pathway; a negative feedback system which suppresses the Th1 cytotoxic immune system. This pathway is often upregulated in cancer, thus promoting a hospitable microenvironment where tumor cells can proliferate. Blockage of the PD-1 pathway has led to notable clinical responses in select patients, but predictive biomarkers are lacking. Early data suggests that colorectal patients with mismatch repair deficient tumors appear to have the best response to immunotherapy therapy. Somatic mutations can be recognized by a patient's own immune system and mismatch repair deficient tumors have 10–100 times more somatic mutations than tumors that are mismatch repair proficient. Based on this rationale a phase II clinical trial was conducted evaluating the activity of an anti-PD-1 agent, pembrolizumab, in 41 patients with progressive metastatic carcinoma with or without mismatch repair deficiency (39). The response rate in patients with mismatch repair deficient colorectal cancer was 40% (95% CI, 12–74%) *vs.* 0% (95% CI, 0–20%) in patients with mismatch repair proficient colorectal cancer.

Trials combining anti-PDI antibodies with anti-CTLA-4 antibiotics are also in development. Cytotoxic T lymphocyte-associated antigen (CTLA-4) is a co-inhibitory molecule that functions to regulate T cell activation. Antibodies that block the interaction of CTLA-4 with its ligands can enhance immune response and increase anti-tumor immunity. Nivolumab is a humanized IgG4 PD-1 blocking antibody and was studied with or without ipilimumab (anti-CTLA-4) in patients with metastatic colorectal cancer in a phase II trial (40). The median PFS for the entire cohort was 5.3 months (95% CI, 1.4–not estimable) in the MMR-deficient patients who received nivolumab single agent therapy, not reached in the MMR-deficient patients who received nivolumab plus ipilimumab, and 1.4 months (95% CI, 1.2–1.90) in the pooled MMR proficient group.

A third anti-PD-1 antibody, atezolizumab, was studied in combination with a MEK inhibitor (cobimetinib) in a phase Ib trial (41). Preclinical models have indicated that targeted inhibition of MEK leads to upregulation of MHC 1 on tumor cells inducting intratumoral T cell infiltration and thus justifying the rationale for this combination. Twenty-three patients were enrolled, the response rate was 17% and serial biopsies indicated PD-L1 upregulation, CD8 T cell infiltration and MHC 1 expression on treatment provide mechanistic rationale.

Future directions

HER2 gene amplifications and activating mutations in the HER1 tyrosine kinase receptor are found in approximately 4–8% of metastatic colorectal cancer. Although not yet standard of care for this disease, preclinical evidence

suggests that colorectal patients with activating mutations may benefit from HER2 directed therapy. The Heracles (Her2 Amplification for colorectal cancer enhanced stratification) trial aimed to assess the activity of trastuzumab and lapatinib in patients with HER-2 positive, KRAS exon 2 wild type colorectal cancer (42). A total of 914 patients were screened, 48 (5%) had HER-2 positive tumors. Of the 27 eligible patients one (4%) had a complete response, seven (26%) had a partial response, and 12 (44%) had stable disease. Additional trials exploring the HER2 pathway are currently in development.

Conclusions

We have seen a significant improvement in patient survival for metastatic colorectal cancer in large part a direct result of novel biologic agents. As we continue to define targets for common mutations we will continue to improve patient outcomes while at the same time minimizing toxicity. Genomic sequencing is now a standard practice at most academic institutions and will become more generalized as mutation dependent studies, i.e., NCI-MATCH trial, continue to emerge. Further research should also focus on predictive biomarkers that can facilitate the enhanced delivery of personalized medicine. Through biologic therapy and targeted agents we can further extend survival and positively impact the devastating course of this common deadly disease.

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Footnote

Conflicts of Interest: MS Noel serves on the speaker's bureau for Taiho Oncolgy.

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