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Biomarkers in the Management of Metastatic Colorectal Cancer- a Mini Review

Joseph Savio Jayaraj*[1,2], Rajesh Naidu Janapala[1,2] and Sanjay Goel[1-3]

[1]*Department of Oncology, USA*

[2]*Montefiore Medical Center, USA*

[3]*Albert Einstein College of Medicine, USA*

***Corresponding author:** Joseph Savio Jayaraj, Department of Oncology, Medical Center, Bronx, USA

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ABSTRACT

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Introduction

Colorectal cancer is the third most common cancer detected in both men and women in the United States. As per American Cancer Society, 101,420 new cases of colon and 44,180 new cases of rectal cancer are expected in the United States, for the year 2019. The lifetime risk of developing CRC is expected to be 1 out of 22 (4.49%) for men and 1 out of 24 (4.15%) for women. In terms of mortality, CRC is the second leading cause of cancer related mortality in both men and women, accounting for 51,020 deaths in 2019 [1,2]. Historically, 5-fluorouracil (5-FU) has been the standard of care for metastatic CRC (mCRC) but following the approval of cytotoxic agents and several targeted therapies in the last two decades, the landscape of treatment of mCRC has changed, leading to increased tumor response and patient survival rates [3]. Cytotoxic agents have been combined with biologic agents in the current standard of care for mCRC. A total of ten different classes of drugs (three classes of cytotoxic agents, six classes of biologic agents, namely anti EGFR, anti-VEGF, multitargeted tyrosine kinase inhibitors, NTRK inhibitors, BRAF inhibitors, MEK inhibitors and one class of immunotherapy) are currently being used for the treatment of mCRC. An overview of all the different drugs that have been approved by the US Food and Drug Administration (USFDA) for use in the management of mCRC, with their mechanism of action and adverse effect profile has been described in Table 1 [4-6].

Table 1: Basal characteristics of colon cancer medications approved by FDA.

Drug	Category	Mechanism of action	FDA indication	Common side effect profile
Class of colon cancer medications – Cytotoxic drugs				
5-Fluorouracil	Antimetabolite (pyrimidine analog)	Non-competitive inhibition of thymidylate synthase	1962: palliative treatment of colon cancer 1st, 2nd line and Salvage therapy; use as a single agent and in combination	Fatigue, stomatitis, nausea, diarrhea, myelosuppression, hyperpigmentation, skin atrophy and hand-foot syndrome
Capecitabine	Antimetabolite (pyrimidine analog)	Prodrug of 5-FU	2001: 1st line when treatment with fluoropyrimidine therapy alone is preferred	Hand foot syndrome, nausea, diarrhea, stomatitis and fatigue.

TAS-102 (Trifluridine / Tipiracil)	A combination of nucleoside analog, and, a thymidine phosphorylase inhibitor	inhibition of thymidylate synthase by the nucleoside analog and prevents degradation of trifluridine via thymidine phosphorylase	third- or fourth-line treatment for metastatic colorectal cancer	combination severe myelosuppression, loss of appetite, diarrhea, nausea, vomiting, fatigue, fever, rashes, itchiness, mouth sores, dizziness, confusion, skin sloughing, numbness, redness and swelling of their palms/soles.
Oxaliplatin	Alkylating agent (platinum)	Inhibits DNA synthesis by forming inter and intrastrand crosslinks with DNA	2002: 2nd line with 5-FU, after irinotecan failure 2004: 1st line with 5-FU	Peripheral neuropathy (acute and chronic), nausea, vomiting, diarrhea, fatigue and myelosuppression
Irinotecan	Camptothecin	Inhibits topoisomerase I, producing DNA breaks	1998: 2nd after failure of 5-FU based therapy 2000: 1st line with 5-FU/LV	2 Dose limiting toxicities: diarrhea (all schedules) and myelosuppression (3- week schedule), Other common side effects: nausea, vomiting, fatigue
Class of colon cancer medications – Biologic/Targeted drugs				
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	Asthenia, diarrhea, hypertension, headaches, stomatitis and leucopenia. Serious Complications: gastrointestinal perforation, impaired wound healing, bleeding and nephritic syndrome
Ziv-aflibercept	Recombinant fusion protein	Binds to VEGF-A, B and placental growth factor (PGF) Inhibits VEGF	2012: In combination with FOLFIRI for patients progressed on oxaliplatin based chemotherapy	Myelosuppression, hypertension, pain, diarrhea, fatigue, skin hyperpigmentation, delayed wound healing
Ramucirumab	Recombinant, human, monoclonal antibody	Antibody against VEGFR2	In combination with FOLFIRI for patients progressed on oxaliplatin based chemotherapy	Hypertension, diarrhea, headache, hyponatremia, neutropenia, nosebleed, intestinal obstruction and arterial blood clots
Regorafenib	Small molecule multi- kinase inhibitor	Binds to the intracellular component of VEGFR-2 and -3, Ret, Kit, platelet-derived growth factor receptor (PDGFR), and Raf kinases Inhibits VEGF	2012: As a single agent salvage therapy for patients with good performance status progressed on other lines	Bleeding gums, cough, myelosuppression, rash, palpitation
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 1st, 2nd line and in salvage setting	Acneiform rash, fatigue, dyspnea, diarrhea and nausea.
Panitumumab	Recombinant, human, monoclonal antibody	Binds to EGFR, inhibiting binding of EGF	2006: single agent on chemo refractory (salvage setting) 2009: amended only for patients with KRAS lacking mutations in codon 12 and 13	Skin rash, hypomagnesaemia, fatigue, nausea and diarrhea
Larotrectinib	Tropomyosin kinase inhibitor NTRK inhibitor	focuses on a specific genetic change called an NTRK fusion	approved as a second line treatment for colorectal cancer who have NTRK fusions, that is metastatic or cannot be removed with surgery and has worsened with other treatments	Tiredness, dizziness, cough, constipation, swelling of ankles/feet/hands, nausea, or vomiting may occur, which can be severe
Dabrafenib	BRAF inhibitor	A BRAF mutation triggers cells to develop abnormally and divide out of control. Targeted therapy drugs block the activity of the mutated BRAF protein	The phase III BEACON CRC trial assessed combining a BRAF, an MEK, and an EGFR inhibitor (encorafenib, binimetinib, and cetuximab, respectively) in metastatic CRC showed that the combination of upstream inhibition with an EGFR inhibitor and downstream inhibition with BRAF and MEK inhibitors was able to target these patients and produce higher response rates	Fever, joint pain, papilloma (warts/ growths), hair loss, hand-foot syndrome (Palmar-planter erythrocythemia), Increased Alkaline phosphatase, rash and back pain

Encorafenib	BRAF inhibitor	A BRAF mutation triggers cells to develop abnormally and divide out of control. Targeted therapy drugs block the activity of the mutated BRAF protein	As above	Nausea, vomiting, diarrhea, headache, tiredness, abdominal pain, joint pain or swelling, dry/itching skin, constipation, or dizziness
Trametinib	MEK inhibitor	A BRAF mutation triggers cells to develop abnormally and divide out of control. Targeted therapy drugs block the activity of the MEK protein	As above	pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.
Binimetinib	MEK inhibitor	A BRAF mutation triggers cells to develop abnormally and divide out of control. Targeted therapy drugs block the activity of the MEK protein	As above	fatigue, nausea, diarrhea, vomiting, abdominal pain, fever, swelling of extremities, and constipation
Class of colon cancer medications – immunotherapy				
Pembrolizumab	Antibody against PD-1	targets PD-1, a receptor on tumor cells, preventing the tumor cells from hiding from the immune system	used to treat metastatic colorectal cancers that have a molecular feature called microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR)	fatigue, cough, shortness of breath, nausea, itching, rash, loss of skin pigmentation (vitiligo) and decreased appetite
Nivolumab	Antibody against Programmed cell death protein 1 (PD-1)	targets PD-1, a receptor on tumor cells, preventing the tumor cells from hiding from the immune system	used to treat metastatic colorectal cancers that have a molecular feature called microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR)	feeling tired, rash, pain in muscles, bones, and joints, itchy skin, diarrhea, nausea, weakness and cough

Predictive Biomarkers

Due to the heterogeneity in mCRC, not all the patients may benefit from the same treatment strategy. Predictive biomarkers can help us to know what will be the likely response of a patient to a particular therapy. Predictive biomarkers can guide the selection of the best treatment strategy for individual patients.

Cytotoxic Agents

We have seen minimal improvements in the biomarkers driven cytotoxic strategies in the past decade. Most known predictive biomarkers for cytotoxic agents are as follows.

DPD Deficiency: Dihydropyrimidine dehydrogenase (DPYD) is a gene encode for the enzyme, dihydropyrimidine dehydrogenase (DPD), a rate-limiting enzyme in the fluoropyrimidine metabolism pathway. Polymorphism in the DPYD gene leads to varying levels of tolerating the fluoropyrimidines (fluorouracil and its oral formulation capecitabine); while a partial or complete deficiency in the DPD activity puts the patient at high risk for developing life-threatening adverse events [7-15]. Particularly the alleles DPYD*2A and A2846T are associated with developing life-threatening severe toxicities in patients receiving fluorouracil or capecitabine therapy [16,17].

TYMS Gene Variations: 5-FU potentially inhibits the enzyme thymidylate synthetase (TS), encoded by the thymidylate synthetase gene (TYMS). TYMS gene has polymorphism for double (2R) or triple (3R) repeat in its promotor region of the gene, which affects the TS levels. It has been observed that patients who are homozygous 2R/2R have low TS levels and may be at higher risk for toxicities up to 1.4 to 2.4 times with 5-FU [18-19]. Currently, there is a commercially available test, namely, "Thera Guide 5-FU". This test may be used to analyze both DYPD gene and TYMS gene polymorphisms but is not routinely seen being done in clinical practice as it is expensive and takes around 7days to report the results.

Micro RNA-143 (miR-143): MicroRNAs regulate the expression levels of other genes by multiple mechanisms. It is observed that low miR-143 expression was associated with longer progression-free survival (PFS) in patients on capecitabine therapy [20]. Contrastingly high miR-143 expression showed longer PFS in patients with 5-FU [21]. It could be understood that the function of miR-143 differs under different circumstances like 5-FU vs. capecitabine. However, its credibility as a biomarker can be established only after further studies. Hence, it is a potential predictive biomarker.

UGT1A1 Polymorphisms: The active metabolite of irinotecan is metabolized by enzyme uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1). This enzyme shows polymorphism with reduced enzymatic activity among those who inherit the UGT1A1*28 allele. A study demonstrated that patients with homozygous and to some extent, heterozygous for allele UGT1A1*28 developed more severe toxicities with irinotecan therapy. However, it also showed

that these patients have better response rates and PFS compared with another allele UGT1A*1 [22].

ABCC5 and ABCG1 Polymorphisms – Irinotecan Toxicity: Polymorphism in the ATP-binding cassette (ABC) genes that participate in the pharmacokinetics of irinotecan were studied. It was observed that the polymorphic transporter genes ABCG1 and ABCC5 were associated with increased risk of developing neutropenia and diarrhea, respectively, in patients treated with irinotecan. This biomarker can potentially further personalize the FOLFIRI treatment of mCRC patients [23].

Topoisomerase 1 Copy Number Alterations: It is known that FOLFIRI and FOLFOX are considered as equally valid as first-line therapy in the mCRC. However, clinicians choose one from their experience or one that they are comfortable managing their toxicities. It has been observed in a study that there is a significant association between the increasing copy number (CN) of topoisomerase 1 (TOP1) and response to irinotecan monotherapy [24] thus suggesting FOLFIRI over FOLFOX in these patients.

Biologic or Targeted Agents

Mutations in RAS

Epidermal Growth Factor (EGF) binding the EGF receptor (EGFR) plays a pivotal role in the regulation of cell differentiation and proliferation by activation of RAS-RAF-MEK-ERK-MAP kinase pathway. Many studies have established that the presence of RAS (KRAS) mutations is predictive of lack of clinical benefit to monoclonal antibodies that bind to EGFR. Besides, they have proven to be harmful when combined with oxaliplatin [25,26]. Therefore, it is recommended that panitumumab and cetuximab (monoclonal antibodies against EGFR) are utilized only in patients with wild type RAS (wt RAS). Results from the PRIME study demonstrated that not only the exon 2 (codon 12 and 13) with seven specific mutations that account for over 90% of KRAS mutations but also KRAS exon 3 (codon 61) and exon 4 (codon 117 and 146), and NRAS mutations also predict for nonresponse to EGFR inhibitor therapy [27]. In addition, it was observed that some patients with wt RAS also did not benefit from anti-EGFR therapy. On further studies, patients with wt KRAS, some miRNAs predicted response to anti-EGFR treatment. Low expression of miR-1881a has been associated with unfavorable outcomes [28-29]. Two tests are FDA approved to test for the mutations in RAS, which include the Cobas KRAS mutation test and Praxis Extended RAS Panel.

BRAF Mutation: The RAF is one of the downstream mediators of the EGFR signaling pathway. Two meta-analyses have revealed that the patients treated with EGFR inhibitors did not show any improvement in terms of PFS or overall survival when compared to chemotherapy alone [30-31]. Based on these results, EGFR inhibitors are not recommended in BRAF mutant patients.

PTPRT and PTPRD: It is observed in a study that deleterious mutation in receptor-type tyrosine-protein phosphatase T (PTPRT), a phosphatase involved in JAK/STAT signaling pathway and its related gene PTPRD correlated with the resistance towards bevacizumab therapy [32]. However, the study involved a tiny sample; hence, more extensive studies must be done to establish the observed effect.

NTRK: In 2018, Larotrectinib, a kinase inhibitor, first of its kind approved for the treatment of malignancies with neurotrophic tyrosine kinase receptor (NTRK) gene fusion without a known acquired resistance mutation, irrespective of the tissue origin of the tumor. NTRK gene fusion happens in only one percent of patients with mCRC; however, in these patients, larotrectinib is a valuable option. Its rarity in mCRC makes it expensive to test and difficult to detect [33].

Immunotherapy Agents

dMMR/MSI-H: Deficient mismatch repair/ Microsatellite instability-high are indicators of genomic instability. Recently, the National Comprehensive Cancer Network (NCCN) guidelines have included nivolumab or pembrolizumab for patients who have progressed following treatment with cytotoxic agents or who are not eligible for cytotoxic combinations. These agents may be used as a second or third line for patients with dMMR/MSI-H positive mCRC [33].

Prognostic Markers

Prognostic markers are biomarkers that give overall progress of a disease in a patient population. Previously, the classical prognostic markers in oncology include the size of the tumor, stage, and presence of metastasis. With the advent of modern molecular techniques and genomic sequencing technology, molecular biomarkers are being discovered which can establish some prognostic value. Table 2 lists out some of the prognostic markers that have been studied and can potentially be used in the clinical practice.

Table 2: Predictive biomarkers which can used in the management of colorectal cancer.

Drugs	Biomarker (Predictive)	FDA approval	Recommended
5-Fluorouracil	Thera Guide 5-FU™	No	No
Capecitabine			
TAS-102			
Oxaliplatin	ERCC	No	No
Irinotecan	UGT1A1	Yes	No
VEGF inhibitors	VEGF SNP	No	No
EGFR inhibitors	KRAS-EXON 2	Yes	Yes
	KRAS-EXON 3,4	No	No
	NRAS-EXON 2,3,4	No	No
	BRAF	No	No
	PIK3CA	No	No
	PTEN	No	No
Regorafenib	None	N/A-	N/A-
Larotrectinib	NRTK	Yes	No
PD-1 inhibitors	MSI-H	Yes	Yes

BRAF inhibitors	p-ERK H	N/A-	N/A-
MEK Inhibitors	p-ERK H	N/A-	N/A-

Conclusion

Although many potential predictive and prognostic biomarkers are being reported in various studies, very few of them are used in the clinical practice due to varying reasons. More clinical studies must be done to identify newer potential biomarkers and to establish the clinical validity of some know biomarkers so that they can be used in clinical practice to individualized treatment options and predict the outcomes.

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