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WORD COUNT	8025	TIME SUBMITTED	20-FEB-2023 02:39PM
		PAPER ID	96793790

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 81922

Manuscript Type: MINIREVIEWS

Systemic treatment for metastatic colorectal cancer

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Abstract

Significant progress has been achieved in the treatment of metastatic colorectal cancer (mCRC) patients during the last 20 years. There are currently numerous treatments available for the first-line treatment of mCRC. Sophisticated molecular technologies have been developed to uncover novel prognostic and predictive biomarkers for CRC. The development of next-generation sequencing and whole-exome sequencing, which are strong new tools for the discovery of predictive molecular biomarkers to facilitate the delivery of customized treatment, has resulted in tremendous breakthroughs in DNA sequencing technology in recent years. The appropriate adjuvant treatments for mCRC patients are determined by the tumor stage, presence of high-risk pathologic characteristics, microsatellite instability status, patient age, and performance status. Chemotherapy, targeted therapy, and immunotherapy are the main systemic treatments for patients with mCRC. Despite the fact that these novel treatment choices have increased overall survival for mCRC, survival remains optimal for individuals with non-metastatic disease. The molecular technologies that are currently being used to support our ability to practice personalized medicine, the practical aspects of applying molecular biomarkers to regular clinical practice; and the evolution of chemotherapy, targeted therapy, and immunotherapy strategies for the treatment of mCRC in the front-line setting are all reviewed here.

Key Words: Systemic treatment; Metastatic colorectal cancer; Personalized medicine; Biomarkers; Chemotherapy; Targeted therapy; Immunotherapy

Leowattana W, Leowattana P, Leowattana T. Systemic treatment for metastatic colorectal cancer. *World J Gastroenterol* 2023; In press

Core Tip: Advances in molecular profiling of metastatic colorectal cancer allow treatment to be tailored to the biologic characteristics of the tumor for certain patient subgroups. Although cures are still rare, more people can expect to live longer. Genomic profiling enables therapy selection, allowing more individuals to benefit while exposing fewer to the harm of ineffective medicines. An important component in determining treatment results is the choice of an effective first-line therapy, which should consider both clinical considerations and molecular indicators. The systemic treatments used in the first-line regimen determine the second-line regimen. Third-line therapy, which includes epithelial growth factor receptor inhibitors for patients with rat sarcoma virus wild-type, should consider molecular profiling. Patients with high microsatellite instability illnesses may be candidates for immunotherapy with pembrolizumab or nivolumab plus ipilimumab

INTRODUCTION

The third most commonly occurring cancer in humans is colorectal cancer (CRC). Over 2 million individuals will be diagnosed with this cancer each year throughout the world. This year, about one million individuals will die from CRC. The liver is the most typical target of CRC hematogenous metastasis, as well as the site most responsible for death from this common malignancy. When patients are diagnosed in the late stages of their diseases, their prognosis remains poor[1,2]. The majority of individuals who have a CRC diagnosis are over 50, while only 12% of all new CRC diagnoses are found in those under 50. Overall, the lifetime risk of developing CRC is around 1 in 23 (4.3%) for men and 1 in 25 (4.0%) for women. According to statistics from the Surveillance, Epidemiology, and End Results Program, at the time of diagnosis, 38% of patients had localized disease, 35% had regional disease, 21% had distant disease, and 6% had no stage[3]. CRC diagnoses have decreased overall since 2000 as a result of increased screening efforts, though it has increased in young people under 50 since the 1990s. Preventive measures, such as routine colonoscopies, remain the most effective way to combat CRC. With a rising interest in non-invasive biomarkers, many additional approaches have been developed. However, nearly 50% of patients were still diagnosed at an advanced stage. Metastatic CRC (mCRC) has a bad prognosis with a 5-year survival rate of 14%, and this number has remained constant over the past 5 years. Until the late twentieth century, mCRC was thought to be always fatal. The discovery that metastatic cancer is mostly localized to the liver in postmortem investigations and radiologic examinations utilizing computer assisted tomography scanners led early pioneers to resect liver metastasis. In order to establish liver resections for metastatic carcinoma as an acceptable treatment, brave pioneers conducted and published data[4]. Only one standard regimen to manage a CRC has been shown to be inefficient, resulting in high rates of treatment failure and disease resistance. Recently, the clinical outcomes of patients with mCRC have improved dramatically as a result of the discovery of prognostic and predictive molecular biomarkers and the subsequent individualization of treatment options. High genetic heterogeneity, including but not limited to chromosomal instability (CIN), microsatellite instability (MSI), and the

CpG island methylator phenotype (CIMP), has been identified by molecular profiling of CRC. Different CRC subtypes have varying prognoses and therapeutic outcomes. Promising improvements for the use of systemic therapy and precision medicine in mCRC have resulted from recent advancements in our understanding of the molecular signaling networks that control intestinal regeneration and homeostasis[5].

The discovery of the key molecular drivers in CRC pathogenesis, coupled with the ability to screen tissue for measurable mutations crucial to disease progression, led to the development of an innovative treatment model for patients with advanced CRC. Despite substantial breakthroughs in tumor biology understanding, these have not entirely translated into proven novel therapies for all patients, since the chemotherapeutic strategy is still built around combination cytotoxic regimens targeted at proliferative epithelium. Although there have been some achievements with targeted therapy, such as the synergistic effect of protein kinase B-Raf (BRAF)-inhibitors and epithelial growth factor receptor (EGFR)-inhibitors in *BRAF*-mutant CRC, certain medications have not been able to offer clinically meaningful improvements for other pathways. As evidenced by the effect of immune checkpoint inhibition in microsatellite unstable CRC, therapeutic exploitation of inter-compartmental signaling in the malignant epithelium may represent an important new drug paradigm in CRC. This is because we are becoming more aware of the signaling crosstalk that controls intestinal cell fate in health and disease, as well as the function of the tumor microenvironment (TME)[6,7].

We have split these important signaling pathways into those that control the destiny of cancer cells or intestinal epithelium directly and those that function indirectly by leveraging the TME in this review. Additionally, we will explore how signaling affects each cancer cell's destiny and comment on some possible treatment prospects that result from effective pathway modulation for each.

RISK FACTORS FOR CRC

Behaviors, diets, and lifestyle

Only a small proportion of CRCs are associated with germline mutations or discovered in the presence of a strong family history; the majority of CRCs are random[8,9]. The significance of environmental exposures has been further demonstrated by the variation in CRC risks throughout the world and the discovery that younger generations are at higher risk of CRC in westernized nations. Numerous studies have been conducted in an effort to identify and quantify the environmental and dietary risk factors for CRC. Global studies show a 45-fold variation in the age-standardized incidence of CRC worldwide[10]. The Gambia and other non-industrialized nations have the lowest rates of CRC, whereas westernized nations have the highest rates. The prevalence of CRC has been seen to rise over time when a nation industrializes and starts to follow a westernized lifestyle and diets low in fiber[11,12]. A westernized diet, or one that is low in fiber, fruits, and vegetables and heavy in processed meats, sugary drinks, and refined grains, is linked to greater risks of CRC. It has been challenging to pinpoint everything that increases the risk of CRC in a westernized diet. This diet's many components are probably a factor in the greater prevalence of CRC. Studies repeatedly show that diets rich in processed foods and red meat are linked to higher risks of CRC. For every 100 g of red and processed meat consumed, CRC incidence increased by 12 percent, according to a recent meta-analysis of 111 studies involving 400 individuals[13] (Table 1). Smoking increases the likelihood of both serrated polyps and colorectal adenomas[14]. According to large observational studies, more pack-years result in higher CRC rates[15]. Recent research suggests that smoking is marginally related to MSI-high (MSI-H) tumors, increases rates of rectal and proximal CRC, and is connected with *BRAF*-mutant malignancies. Similar to smoking, drinking alcohol is a recognized risk factor for CRC, and recent pooled studies have demonstrated that even occasional drinking increases the risk of CRC[16].

Numerous studies have shown that an increased risk of CRC is related to obesity and decreased physical activity. CRC has repeatedly proven to be correlated with excess body fat, which is most typically quantified using BMI and waist circumference. Sedentary activity, such as extended sitting or TV viewing, is linked to a higher risk of CRC. In populations over 50, the majority of research verifying obesity and a lack of

physical exercise as risk factors for CRC has been demonstrated. Attempts to quantify the impact of obesity and physical activity on rates of early-onset CRC have rekindled attention in light of the rising burden of young-onset CRC in developed nations[17,18]. These and other investigations support the advice from the American Cancer Society and other cancer organizations that maintaining a healthy weight and engaging in more physical exercise are crucial for lowering the risk of CRC.

Genetic factors

A family history of cancer without a specific condition is thought to be the cause of 25% of CRCs, while hereditary cancer syndromes are thought to be the cause of 5% of CRCs. The hereditary component of CRC is predicted to be 35%-40%. Hereditary non-polyposis colorectal cancer (Lynch syndrome), familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP) are the most prevalent hereditary cancer syndromes. About 2%-4% of all CRCs are caused by Lynch syndrome, the most prevalent hereditary CRC condition. Patients with Lynch syndrome are susceptible to endometrial, ovarian, stomach, small intestine, hepatobiliary tract, pancreatic, ureter, and renal pelvis malignancies. Lynch syndrome is caused by mutations in the DNA mismatch repair genes *hMLH1*, *hMSH2*, *hMSH6*, and *hPMS2*[19,20]. The lifetime risk of CRC for these people is between 5% and 85%. FAP makes up roughly 1% of colorectal cancer cases and is the second most prevalent hereditary colorectal cancer syndrome. A germ line mutation in the adenomatous polyposis coli (*APC*) gene that causes a shortened APC protein is the secondary cause of FAP. With a 90% inheritance, it is inherited in an autosomal dominant manner. For these people, thousands of polyps form in the gastrointestinal system, the majority of which are in the colon. By the third or fourth decade, CRC will manifest in all FAP-affected individuals without preventative colectomy[21]. The lifetime risk of CRC for these MAP individuals is expected to be 43%-100%. Serrated polyposis syndrome, Peutz-Jeghers syndrome, and juvenile polyposis syndrome are further polyposis syndromes associated with a higher risk of CRC. These are all uncommon disorders that together only contribute to 1% of CRC incidence. Race, age, and sex are other unmodifiable risk

factors for CRC in addition to family history. Male patients are generally at a higher risk of developing CRC than female patients; ideas explaining this include the fact that women typically have less visceral fat and benefit from estrogen's general preventive properties against CRC. Men are also less likely to pursue screening, and they may be more exposed to environmental risks, including drinking, smoking, and unhealthy diets[22].

Polyps

Most CRCs develop from a harmless precursor polyp. Therefore, people who have a considerable personal or family history of high-risk polyps are at a higher risk of developing colorectal cancer. There are many different forms of polyps, some of which are non-neoplastic, including hyperplastic polyps, mucosal polyps, inflammatory polyps, and harmartomatous polyps. The remaining polyps, including adenomatous and serrated polyps, have cancerous potential. Adenomatous polyps are where the vast majority of sporadic CRCs originate. By the time they are 50, roughly one-third of individuals are predicted to develop polyps. However, the majority of these won't move on to CRC. Villous histology, high-grade dysplasia, and polyps larger than 1 cm all enhance the likelihood that they may develop into CRC. Serrated polyps are believed to be antecedents for up to 10%-15% of sporadic CRCs, albeit less frequent[23,24].

COLORECTAL CARCINOGENESIS

Three molecular pathways have been hypothesized for colorectal carcinogenesis, two of which center on the growth of polyps into cancerous tumors. The traditional pathway depicts the long-term evolution of normal cells to adenomas and finally to carcinomas (the adeno-carcinoma sequence). This causes 85%-90% of all sporadic CRC and is mostly related to the growth of tumors that are CIN. It is frequently accompanied by an early *APC* gene mutation, activation of the growth-promoting oncogenes Kristin rat sarcoma virus (*KRAS*) or *BRAF*, and additional mutations that cause cancer to proceed. About 10%-15% of sporadic CRCs are caused by the CIMP/serrated pathway[25,26]. Due to these

changes in the methylation of gene promoter regions and general hypomethylation, many genes are silenced. Early BRAFV600E mutations are frequently seen in these tumors, which activate the mitogen activated protein kinase (MAPK) pathway and cause the growth of hyperplastic polyps[27]. The MSI-H pathway is the third route. Over 95% of the malignancies related to Lynch syndrome are caused by this important pathway. Outside of Lynch syndrome, MSI is a rare condition that is caused by a lack of DNA mismatch repair genes, which eventually results in altered DNA sequences (Figure 1).

KRAS

A proto-oncogene called *KRAS*, which produces a GTPase protein, is essential for intracellular signal transduction downstream of membrane-bound receptors like the EGFR. Uncontrolled cell growth, proliferation, survival, migration, and invasion ensue from a mutation in *KRAS* because it causes constitutive activation of the MAPK pathway regardless of independent activation of the upstream EGFR receptor. Activating *KRAS* mutations have been reported in a variety of cancers and have been found in between 30 and 50 percent of CRC patients[28,29]. *KRAS* is a crucial biomarker for prognosis and prediction in the management of mCRC. *KRAS*-mutated tumors in mCRC have a poorer prognosis and are more likely to exhibit aggressive biology, spread metastatically, recur, and result in mortality. *KRAS* mutation was independently linked to poorer progression free survival (PFS) and overall survival (OS) in individuals who underwent hepatic resection for mCRC, according to data from those patients. *KRAS* codon 12 has been linked to lower recurrence-free survival in variations of *KRAS* mutations throughout all stages of mCRC[30]. Data suggest that curative resection may not be advantageous in the metastatic scenario in *KRAS* mutant patients who also have other poor clinical prognostic characteristics, such as node-positive disease or extensive metastases, due to the prognostic consequences of *KRAS* mutations[31]. Additionally, the existence of a *KRAS* mutation acts as a biomarker for the therapeutic efficacy of some therapies, such as EGFR inhibitor therapy. Anti-EGFR treatment has been shown to be effective in treating KRAS wild-type (KRAS WT) cancers in several clinical studies. Due to the independent

constitutive activation of KRAS downstream of EGFR, which persistently encourages cell growth and division, anti-EGFR treatment is not helpful in patients with *KRAS* mutations[32]. Although EGFR inhibition is effective in treating the majority of KRAS WT tumors, some patients continue to have resistance, necessitating more research. Mutations in other RAS family oncogenes, such as neuroblastoma RAS (NRAS) and Harvey RAS, identify tumors that are resistant to anti-EGFR treatment. Other phosphorylation pathway genes that work downstream of EGFR, such as phosphoinositide 3-kinases, phosphatase and tensin homolog, MAPK, and mitogen-activated protein kinase (MEK), have not demonstrated to be accurate predictors of EGFR response for mCRC, and research into the causes of anti-EGFR resistance in this patient group is still underway[33].

BRAF

BRAF, a serine/threonine-protein kinase, is an essential component of the MAPK cell signaling cascade downstream of KRAS. In fewer than 10% of CRC patients, *BRAF* mutations have been found. The same MAPK pathway that KRAS uses for BRAF signaling also uses it, and functional mutations in either of these genes have identical effects on phenotypic and treatment implications. As a predictive biomarker for mCRC, the *BRAF* mutation is linked to worse outcomes, shorter survival, and a greater incidence of peritoneal and distant lymph node involvement. In patients with mCRC undergoing curative-purpose hepatectomy, the *BRAF* mutation was associated with poorer survival compared to both *BRAF* WT and *KRAS* mutated tumors[34,35]. BRAF also functions as a prognostic marker. Vemurafenib, a direct BRAF inhibitor, was first discovered through early attempts at targeted medication treatment for melanoma. Studies were done to examine if BRAF inhibition has a comparable effect on colorectal cancer. BRAF inhibition and EGFR inhibitors together produced an OS improvement. In patients with *BRAF* mutant mCRC, encorafenib in conjunction with EGFR inhibition is a potent form of newer generation BRAF inhibition therapy[36].

Human epidermal growth factor 2

A further alluring target for mCRC is human epidermal growth factor 2 (HER2), which is essential for intracellular signal transduction. It is generally known that HER2 plays a role in the development of breast cancer and that trastuzumab and other HER2 inhibitors can be used to treat the disease specifically. Because there are so many targeted treatments available, many researchers have concentrated on HER2 mutations in the mCRC population, despite the fact that only a tiny percentage of patients (10%) overexpress HER2. Trastuzumab with pertuzumab, trastuzumab with lapatinib, and Fam-trastuzumab deruxtecannxki are now available as HER2 inhibitors. Even though it only accounts for a small proportion of all mCRC patients, the HER2 amplified condition serves as a predictive biomarker for HER2 targeted therapy with the potential for therapeutic response[37-39].

SYSTEMIC TREATMENT FOR MCRC

A surgeon may be able to completely remove a few metastatic foci of mCRC, which are often located in the liver or lung. When the main tumor and all metastases can be completely removed surgically, mCRC is said to be resectable. However, nodal infiltration and covert micrometastatic spread are frequent in these individuals. Less than 20% of individuals with mCRC who undergo resection are permanently cured. Oncologists from the surgical and medical branches should work together to develop treatment strategies when mCRC may be resectable. If the main tumor is in the rectum, radiation oncologists should be consulted. The main therapy for mCRC is systemic chemotherapy. The United States Food and Drug Administration (FDA) has authorized many medications for the treatment of mCRC. However, for the majority of patients, mCRC is still incurable. Despite the rarity of a cure for mCRC, recent major clinical trials with patients who could tolerate chemotherapy have demonstrated that patients can live for two to three years with intense treatment and numerous systemic medicines. Survival is influenced by the molecular subtype, which provides information about the prognosis by describing the natural history of a tumor and the therapies that are and are not likely

to be successful. The median OS for the 50% of patients with KRAS/NRAS/BRAF WT mCRC is about 30 mo with survival rates of 80% at 1 year, 40% at 3 years and 20% at 5 years after start of first-line chemotherapy (Table 2).

SYSTEMIC TREATMENT FOR LIVER METASTASIS CRC

Nearly half of individuals with initial CRC develop liver metastatic diseases from CRC or colorectal liver metastasis (CLM). The resectability of CLM determines how to manage it, and interdisciplinary approaches are frequently used. Conversion treatment (CT), a kind of systemic treatment, is used for liver metastases that are initially incurable. Both the number (4 *vs* > 4) and the size (diameter < 6 cm *vs* ≥ 6 cm) of CLMs are independent variables linked to successful CT[40,41].

Targeted treatment

FOLFOX [5-fluorouracil (5-FU), leucovorin, and oxaliplatin] and FOLFIRI (5-FU, leucovorin, and irinotecan) are the mainstays of systemic chemotherapy used to treat mCRC. EGFR inhibitors (EGFRi) for RAS WT tumors [cetuximab (Cet) and panitumumab (Pan)] and anti-VEGF [bevacizumab (Bev)] are the two main groups of medications now added to these chemotherapy regimens.

Resectable CLM with no extra-hepatic metastasis

There is debate regarding the benefits of adding a targeted treatment, however, the addition of Bev or Cet to FOLFOX or FOLFIRI is tolerable in resectable liver metastases. However, a single-arm Phase II study found that the addition of Bev to the capecitabine and oxaliplatin combination (CAPOX) (six cycles with no Bev on the final cycle), before surgery in high-risk CRC, had a remarkable objective response rate (ORR) of 73%[42]. In 2020, Bridgewater *et al*[43] conducted a multicenter, open-label, randomized, controlled, phase 3 trial to investigate the effects of Cet plus chemotherapy compared with those given chemotherapy alone in 257 adult patients (aged ≥ 18 years) with KRAS WT (codons 12, 13, and 61) resectable or sub-optimally resectable. At a median follow-up of 66 mo

after the last patient was recruited, this analysis was conducted. In the chemotherapy alone group, the median PFS was 22.2 mo, while in the chemotherapy plus Cet group, it was 15.5 mo (P = 0.304). In the chemotherapy alone group, the median OS was 81.0 mo, but in the chemotherapy plus Cet group, it was 55.4 mo (P = 0.036). The status of pathological resection or the preoperative response were secondary outcomes that did not significantly differ between groups. High-risk CRC in this study included those with synchronous liver metastases, metastatic disease discovered within a year of initial resection, primary tumors with positive lymph nodes, CLMs > 1 or > 5 cm, and positive carcinoembryonic antigen (CEA) levels. They concluded that Cet had no effect when used with perioperative treatment. As a result, targeted therapy is deemed ineffective in CRC patients with resectable CLM, whereas Bev may be beneficial in high-risk patients. FOLFOX adjuvant treatment is advised following resection.

Unresectable CLM with potential for resection and no extra-hepatic metastasis

In high-risk CRC (> 4 metastases, diameter > 5 cm, poor viable liver function if undertaking upfront resection, or inability to maintain liver vascular supply), neoadjuvant treatment (NAT) with CAPOX plus Bev achieved a 78% ORR[44]. Out of the 46 patients included, 40% of the individuals with unresectable disease upon diagnosis got a resection. Four patients responded so well that they were kept under surveillance without having surgery. In comparison to FOLFOX, Bev with FOLFOXIRI (combination of 5FU/LV, oxaliplatin, and irinotecan) had a greater resection rate (61% *vs* 49%), R0 resection rate (49% *vs* 29%), ORR (81% *vs* 62%), and mean PFS (18.6 m *vs* 11.5 m)[45]. After a hepatic artery infusion chemotherapy pump has been installed, adding Bev to the chemotherapy has no survival benefit. On the other hand, it worsens liver toxicity (hyperbilirubinemia > 3 mg/dL) and is not advised[46]. In the POCHER study, 60% (25/43) of the 43% of patients with unresectable CLM who received chronomodulated irinotecan (Iri) and 5FU/LV on days 2-6 every two weeks as NAT experienced full resections[47]. Twenty-nine participants with more than 4 lesions and 9 patients with more than 5 cm in diameter made up the study population. The 2-year survival rate was 68%

for the whole population. In people who have had surgery, it may reach 80%. As a result, research was conducted to evaluate the role of EGFRi in NAT or POT. When Cet was given to FOLFOX or FOLFIRI in patients with unresectable CLM at diagnosis who were eligible (with KRAS WT codons 12, 13, and 61), it improved long-term survival[48].

Unresectable CLM

First-line plus chemotherapy: Bev is advised as the first-line treatment for RAS-mutated tumors in mCRC with CLM and without surgical consideration. A meta-analysis of two randomized control trials and three observational studies revealed that Cet had a higher OS, ORR, and complete response rate than Bev in RAS-WT malignancies (with chemotherapy as the backbone). The same trial found no appreciable differences between the two medications in PFS, disease control rate, or partial response rate[49]. In the PEAK study, Pan outperformed Bev in terms of PFS while maintaining the same OS[50]. In the past five years, a lot of research has been done on the function of the main tumor side (right *vs* left). Regardless of the CLM status, two meta-analyses have conclusively demonstrated that left-sided cancers react better to EGFRi than Bev[51,52]. However, there was no statistically significant difference in OS or PFS between Bev and EGFRi in tumors on the right side. In the PEAK study and the FIRE-3 trial, EGFRi with chemotherapy produced deeper responses in RAS-WT tumors than Bev plus chemotherapy. Tolerability is a crucial consideration when choosing a medication. Patients with a history of thromboembolic illness, uncontrolled hypertension, proteinuria, significant bleeding risk, or gastrointestinal perforation are not advised to get anti-VEGF medication. As a result, EGFRi (Cet or Pan) is preferable over Bev plus chemotherapy in left-sided tumors in RAS-WT mCRC with CLM, although either of them can be administered in right-sided tumors[53,54]. There isn't any conclusive proof that Pan or Cet is superior to the other. Patients who experience adverse reactions to Cet, a mouse-based monoclonal antibody (mab), frequently prefer Pan since it is a humanized mab.

Second-line plus chemotherapy: The continuation of Bev in the second line after first-line treatment improved PFS and OS without a worsening in side events. There is insufficient information to definitively conclude that changing eligible patients from Bev to Cet or Pan following clinical progression would be beneficial[55,56]. T There is no advantage to switching Bev to another VEGF medication. Patients who progress on oxaliplatin-based therapy (FOLIRI-naive) benefit from ziv-aflibercept or ramucirumab when used in conjunction with FOLIRI[57]. Bev may also be used in the third or fourth line of TAS-102 (trifluridine and tipiracil hydrochloride)[58]. Continuing EGFRi has no advantage for OS if Cet or Pan are used as the first-line treatments[59]. Circulating tumor DNA can be used to identify acquired resistance, which may manifest in a small number of patients. It is anticipated that this resistance would fade with time. As a result, switching to Bev is advised[60,61]. After the disease progressed, switching from Cet to Pan or vice versa is not useful. If not used in the first-line setting, EGFRi may be administered either alone (monotherapy) or with Iri, FOLFIRI, or FOLFOX, but not with CAPEOX, or to patients who cannot handle chemotherapy[62]. In ongoing studies, they are being used with additional medications such as immune checkpoint inhibitor (ICI), BRAF, and tyrosine kinase inhibitors.

Patients with resistant mCRC who have *BRAF* mutations, notably BRAF V600E and KRAS WT, may benefit from a combination therapy that combines BRAF inhibitors with Cet or Pan[63]. In the interim-analysis of the BEACON trial, triple treatment with the MEK inhibitor (Binimetinib) demonstrated a survival benefit over the control group (Cet plus Iri or FOLFIRI) and combination therapy. A more recent investigation, however, found no benefit of triplet treatment over doublet treatment compared to the control group[64]. In the initial studies with Pan, other BRAF inhibitors, dabrafenib and vemurafenib, with/without MEK inhibitors (trametinib), showed favorable outcomes[65]. In approximately 6% of CRCs, HER2 is amplified or overexpressed[66]. Trastuzumab, a HER2 inhibitor, in combination with pertuzumab (a mab that prevents dimerization of HER2 and HER3) or lapatinib (inhibitor that binds to the cytoplasmic ATP-binding site inhibitor EGFR/HER1 and HER2 receptors), is well tolerated in refractory mCRC

patients with HER2 amplification and RAS/BRAF WT[67]. HER2-amplified, a humanized anti-HER2 antibody combined with a topoisomerase I inhibitor, known as trastuzumab deruxtecan (T-dx), demonstrated an excellent ORR (45.3%) after a median follow-up of 27.1 wk in refractory mCRC[68]. Patients who were resistant to HER2 inhibitors also showed activity when given T-dx. Neurotropic tyrosine receptor kinase (*NTRK*) genes code for the tyrosine kinase receptors that control cell growth, and rearrangements result in unregulated cell proliferation. It was first discovered in CRC and occurs in just 0.3% of solid tumors[69]. There was 7% CRC in the studies that administered NTRK inhibitors to solid tumors, such as entrectanib and larotectinib. Patients with *NTRK* mutations may choose this as a treatment option[70].

A multinational, randomized, placebo-controlled, phase 3 trial of a multikinase tyrosine kinase inhibitor is called the CORRECT trial. The regorafenib therapy group outlived the placebo group by 1.4 years (mOS for regorafenib is 6.4 years *vs* 5 years for placebo, $P = 0.005$). The use of a regulator was associated with higher medication toxicity (93% in the regorafenib *vs* 61% in the placebo). Hand-foot skin reactions were the most common adverse event (83%) observed, followed by tiredness (48%) and hypertension (36%). ICIs including ipilimumab/nivolumab, pembrolizumab, and EGFRi are now being explored in conjunction with it. Its usage is frequently contrasted with that of the TAS-102, which had an OS improvement of 1.8 m above placebo. Combinations of ICI and EGFRi are being investigated[71] (Figure 2).

IMMUNOTHERAPY

The goal of immunotherapy is to use the immune system to fight cancer. For patients with mCRC that is mismatch-repair-deficient (dMMR) or MSI-H (dMMR/MSI-H mCRC), immune checkpoint inhibitors (ICIs) have emerged as a very effective treatment. ICIs modify the interaction of T cells, antigen-presenting cells, and tumor cells to help unleash suppressed immune responses. The FDA approved pembrolizumab and nivolumab (with or without Ipilimumab) for the treatment of these patients due to their effective, stable, and long-lasting responses. The fundamental difficulty is to offer the

advantage of immunotherapy to the great majority of mCRC patients who are mismatch-repair-proficient (pMMR), microsatellite-stable (MSS), or have low MSI (MSI-L), since mCRC is characterized by an inadequate number of mutant tumor antigens[72].

ICIs-based immunotherapy

Use of ICIs in DMMR/MSS mCRC: To preserve DNA integrity, MMR is essential. CRC can be classified as dMMR or pMMR CRC based on the detection of the MMR proteins MLH1, MSH2, MSH6, or PMS2 utilizing immunohistochemical staining. Moreover, insertions and deletions can cause MSI, which can be precisely identified by PCR or next-generation sequencing, resulting in a change in microsatellite length. Major histocompatibility complex (MHC) class I-peptide complexes, including mutant peptides that might be identified as neoantigens and subsequently increase immune cell priming and infiltration, are present on the surface of tumor cells in dMMR-MSI-H malignancies. T helper 1 CD4+ T cells, macrophages, and CD8+ tumor-infiltrating lymphocytes (TILs) enter the TME and produce IFN-g. Programmed cell death ligand-1, CD80, and CD86 of the B7 family are examples of T cell inhibitory ligands that dMMR-MSI-H tumor cells persistently upregulate to support immune escape[73-75]. The percentage of dMMR-MSI-H CRCs, which accounts for around 15% of all CRCs, is correlated with tumor stage. dMMR-MSI-H cancers make up around 5%-20% of stage 2 and 11% of stage 3, but only 5% of stage 4. Additionally, dMMR-MSI-H is a predictive biomarker for individuals at various phases of their condition. Patients with dMMR-MSI-H tumors had a much better prognosis than those with pMMR-MSI-L cancers in stages 2 and 3. Surprisingly, individuals with stage 4 dMMR-MSI-H have a poor prognosis yet respond well to immune checkpoint inhibition[76,77].

Le *et al*[78] conducted a phase 2 trial in 41 patients with progressive mCRC with or without dMMR to investigate the clinical efficacy of pembrolizumab, an anti-Programmed cell death protein 1 (PD-1) ICI, in 2015. Pembrolizumab was given intravenously every 14 d at a dosage of 10 mg/kg BW to patients with dMMR CRC, pMMR, and patients with dMMR who were not colorectal. The immune-related ORR and

PFS for dMMR CRC were 40% and 78%, respectively, and 0% and 11% for pMMR CRC. In the group with dMMR CRC, the median PFS and OS were not attained, but in the cohort with pMMR CRC, they were 2.2 and 5.0 mo, respectively [hazard ratios (HR) for PFS and death = 0.10 and 0.22]. Responses in patients with dMMR non-CRC were comparable to those in individuals with dMMR CRC. High somatic mutation loads were related to longer progression-free survival ($P = 0.02$), and whole-exome sequencing found that dMMR tumors had an average of 1782 somatic mutations per tumor, compared to 73 somatic mutations in pMMR tumors ($P = 0.007$). They concluded that MMR status predicted the therapeutic benefit of immune checkpoint inhibition with pembrolizumab (Figure 3).

In 2020, the KEYNOTE-164 study analyzed pembrolizumab's effectiveness in 124 patients with dMMR/MSI-H mCRC who had undergone treatment. The ORR was 32% among the 63 patients examined, and the median PFS was 4.1 mo. The overall median survival rate has not yet been reached. The percentages of OS and PFS at one year were 41% and 76%, respectively. A single ICI therapy for individuals with dMMR/MSI-H mCRC demonstrated sustained anticancer efficacy[79]. In a phase III, open-label study, 307 mCRC patients with dMMR/MSI-H who had not previously received treatment were enrolled to assess the effectiveness of PD-1 blockers or chemotherapy as first-line treatments. They were given a 1:1 random assignment to undergo chemotherapy (5-FU-based treatment with or without bevacizumab or cetuximab) every 2 wk, or pembrolizumab at a dosage of 200 mg every 3 wk. After the advancement of the condition, patients taking chemotherapy could switch to pembrolizumab therapy. Of the 307 patients enrolled, 153 received single-agent pembrolizumab and 154 received chemotherapy. The median progression-free survival time was 16.5 mo in the pembrolizumab group and 8.2 mo in the chemotherapy group at a median follow-up of 32.4 mo (HR = 0.60, $P < 0.001$) Significant differences were seen between the pembrolizumab group's 12-mo and 24-mo progression-free survival values, which were 55% and 48%, respectively, *vs* 37% and 19% in the chemotherapy group. These data show that, as compared to chemotherapy, pembrolizumab demonstrates more stable

anticancer activity and fewer treatment-related adverse events[80]. Based on the compelling evidence from this trial, the FDA approved pembrolizumab for the first-line treatment of patients with dMMR/MSI-H or advanced, unresectable, or metastatic colorectal cancer in June 2020.

In certain clinical studies, the use of nivolumab, another PD-1 inhibitor that targets dMMR/MSIH CRC, is also being investigated. Nivolumab's effectiveness was examined in the phase 2 study CheckMate 142 on 74 patients with dMMR/MSI-H mCRC. The ORR was 31%, and 69% of patients had disease control for 12 wk or longer. The median duration of response was not attained. The PFS and OS rates during the past 12 mo were 50% and 73%, respectively. Nivolumab's safety profile in this cohort study was consistent with that previously reported in other solid tumor trials, and there were no additional adverse events noted[81]. Nivolumab was approved by the FDA in August 2017 for the treatment of dMMR/MSI-H mCRC in adults and children older than 12 years old on the basis of these research findings[82]. Nivolumab's administration in conjunction with the cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody ipilimumab was also investigated in the CheckMate142 trial. Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg was given once every three weeks (four doses) to a total of 119 patients with dMMR/MSI-H mCRC who had not responded to conventional therapy. Nivolumab 3 mg/kg was then given once every two weeks. The ORR was 55% at a median follow-up of 13.4 mo. In 80% of patients, the disease was under control for at least 12 wk, however, the median PFS was not met. The PFS rates for the 9th and 12th months were 76% and 71%, respectively. The 9-mo and 12-mo OS rates were 87% and 85%, respectively, but the median OS was not met[83]. The FDA expedited the approval of nivolumab in combination with ipilimumab for the treatment of patients with dMMR/MSI-H mCRC in July 2018 based on the findings of this trial. Furthermore, the most recent information from the 2-year follow-up was used to update the study outcomes. The ORR and disease control rates determined by the study were 69% and 84%, respectively, over the median follow-up of 29 mo. The 2-year PFS and OS rates were 74% and 79%, respectively, but the median PFS and OS were not attained[84].

After first-line chemotherapy failed, Kim *et al*[85] conducted a prospective, open-label, multicenter phase II trial in 2020 to assess the effectiveness and safety of avelumab in 30 mCRC patients who had dMMR)/MSI-H and 3 mCRC patients who had Polymerase-epsilon (POLE) mutations. All of the respondents were dMMR/MSI-H, and the ORR was 24.2%. At a median follow-up time of 16.3 mo, the median PFS and OS for all patients were 3.9 and 13.2 mo, respectively. They concluded that in patients with previously treated mCRC carrying dMMR/MSI-H, avelumab demonstrated anticancer efficacy with controllable toxicity. In order to assess the effectiveness and safety of cetuximab re-challenge treatment combined with avelumab in 71 MSS, 3 MSI-H, and 3 patients with uncertain microsatellite status with mCRC, Martinelli *et al*[86] undertook a single-arm, multicenter phase 2 study in 2021. The patients were given cetuximab (400 mg/m^2, then 250 mg/m^2 weekly) and avelumab (10 mg/kg every two weeks) until the disease progressed or the side effects became intolerable. With a median OS of 11.6 mo and a median PFS of 3.6 mo, the trial accomplished its primary aim. Four percent of grade 3 adverse events were diarrhea, and 14% of them were skin eruptions. There were 48 people with WT illnesses and 19 people with mutations. Those with RAS/BRAF WT cDNA had a median OS of 17.3 mo, as opposed to patients with mutations, who had a median OS of 10.4 mo. In contrast to patients with mutant cDNA, those with RAS/BRAF WT had a median PFS of 4.1 mo as opposed to 3.0 mo. They concluded that an active, well-tolerated challenge treatment for RAS WT mCRC is cetuximab plus avelumab.

Use of ICIs in PMMR/MSS mCRC: pMMR/MSS CRC, which makes up around 95% of all mCRCs, is referred to as a "cold tumor". Single-agent ICI had no effect on pMMR/MSS CRCs, in contrast to inflammatory tumors of dMMR/MSI-H. The results of recent investigations on the use of combination ICIs have raised the prospect of enhancing immunotherapy efficacy in this population. ICIs in conjunction with systemic chemotherapy were proven to dramatically increase tumor treatment response in refractory mCRC treated with conventional chemotherapy and immunotherapy, especially in pMMR/MSS CRCs. Existing data shows that immunogenic chemotherapy

might improve the efficacy of ICIs by increasing tumor infiltration of CD4+ and CD8+ T cells and interrupting the function of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells[87,88]. In order to investigate ways to make cold tumors heated to boost sensitivity to immunotherapy, a number of ICI-based combination treatment studies tested ICIs in conjunction with chemotherapy, targeted therapy, ICI therapy, and radiation.

Pembrolizumab combined with modified FOLFOX6 was tested in a single-arm, multicenter phase 1b study by Herting *et al*[89] for the treatment of mCRC. In this study, 87% of the participants had pMMR/MSS mCRC. At a median follow-up of 19.9 mo among the 30 patients, the investigators noted an ORR of 57% and the mean time it took for the responding patients to respond was 37.57 wk. The median PFS time was 8.8 mo, and the median OS was not reached. Recently, two phase II trials, AtezoTRIBE and MAYA, evaluating combinations of ICIs with chemotherapy, revived optimism for the use of immunotherapy in pMMR/MSS mCRC patients, indicating a significant breakthrough and a potential basis for future research in this scenario.

AtezoTRIBE trial: Regardless of microsatellite status, 218 patients with unresectable and chemo-naive mCRC were randomized in a 1:2 ratio to receive FOLFOXIRI. The control group received first-line FOLFOXIRI (intravenous 165 mg/m² irinotecan, 85 mg/m² oxaliplatin, 200 mg/m² leucovorin, and 3200 mg/m² fluorouracil as a 48-hour infusion) plus bevacizumab (5 mg/kg intravenously), and the atezolizumab group received the same regimen plus atezolizumab (840 mg intravenously) in the AtezoTRIBE phase II multicenter, open-label, comparative study. According to the randomized arm, both treatments were given for up to 8 cycles, then 5-FU with bevacizumab, with or without atezolizumab, was given until the condition progressed, there were unacceptable side effects, or the patient withdrew their consent. PFS was the main endpoint, with a 1-sided alpha error of 0.10 and an 85% power. A median follow-up of 19.9 mo was being used. In the atezolizumab group, the median PFS was 13 1 mo, compared to 11.5 mo in the control group (HR = 0 69; *P* = 0 012). Neutropenia (42% of 142 patients in the atezolizumab group

vs 36% of 72 individuals in the control group), diarrhea (15% *vs* 13%), and febrile neutropenia (10% *vs* 10%) were the most common all-cause grade 3-4 adverse events. A total of 39 patients (27%) in the atezolizumab group and 19 patients (26%) in the control group suffered serious adverse events. Acute myocardial infarction and bronchopulmonary hemorrhage caused two (1%) treatment-related fatalities in the atezolizumab group; none were recorded in the control group. They concluded that first-line FOLFOXIRI plus bevacizumab with atezolizumab added was safe and enhanced PFS in patients with mCRC who had not previously received treatment[90].

MAYA trial: MAYA is a prospective single-arm phase II trial that included patients with chemo-resistant mCRC who had centrally confirmed MSS status, O6-methylguanine-methyltransferase (MGMT) silence determined by promoter methylation of the MGMT gene, and total immunohistochemical loss of MGMT protein. Only in situations where disease control is obtained during phase I are participants to receive two cycles of temozolomide (TMZ) (phase I), followed by the addition of nivolumab and low-dose ipilimumab (phase II). The 8-mo PFS rate in patients included in phase II of the trial served as the study's main objective. The MAYA trial's design is supported by an intriguing biological theory. In short, the MGMT gene plays a role in repairing DNA damage brought on by alkylating drugs like TMZ[91]. Sensitivity to TMZ is increased when MGMT is inactivated by hypermethylation of its promoter. As demonstrated in studies evaluating the efficacy of TMZ alone or in combination with other chemotherapeutic agents, such as capecitabine and irinotecan, retrospective data revealed that sensitivity to TMZ was primarily restricted to pMMR/MSS tumors with complete MGMT protein loss detected with immunohistochemistry[92]. After the first disease response, MGMT re-expression, the selection of sub-clones that express MGMT, or a hypermutated condition resulting from acquired mutations in MMR genes that might make mCRC sensitive to ICIs can all lead to secondary resistance to TMZ[93]. In the MAYA study, 204 of 703 assessed patients (29%) were found to be molecularly suitable. Overall, 142 out of 703 (19%) patients were enrolled in phase I, with just 33 (5% of the

initial 703 screened patients) progressing to phase II. The 8-mo PFS rate was 36% after a median follow-up of 23.1 mo. The median PFS and OS were 7.0 and 18.4 mo, respectively, with a 45% response rate. Skin rash (6%), colitis (3%), and hypophysitis (3%), were all immune-related side effects of grade 3-4 severity. There were no unanticipated adverse events or treatment-related fatalities recorded. They concluded that TMZ priming followed by a combination of low-dose ipilimumab and nivolumab might result in long-term therapeutic benefit in MSS and MGMT-silenced mCRC. These findings should be considered with caution due to the lack of a control arm testing the effectiveness of TMZ monotherapy, which prevented the investigators from distinguishing the effect of immunotherapy addition *vs* TMZ alone. Given that not all patients who are initially susceptible to TMZ develop a hypermutated phenotype, only a subset of individuals may benefit from immunotherapy. Future analyses separating the ORR observed during phase I (with TMZ) from the ORR reported during phase II (with TMZ plus ipilimumab plus nivolumab), as well as current translational investigations, might reduce this issue.

Despite the need for more mature follow-up data, the good findings from the AtezoTRIBE and MAYA trials bring an end to a long period of stagnation and dismal outcomes in the landscape of immunotherapy in pMMR/MSS mCRC. In the first-line scenario, chemotherapy escalation and TMZ delivery in MGMT-silenced chemo-refractory patients are capable of sensitizing immune-deficient or cold mCRCs to immunotherapy, perhaps rewiring an inflamed/hot TME, then unleashed against the tumor by ICIs. Larger confirmatory and translational trials, however, are required to identify people who benefited the most from these therapies[94].

ADOPTIVE CELL THERAPY

Adoptive cell therapy (ACT), a crucial component of tumor immunotherapy, entails the introduction of immunologically active cells that have been grown and altered *in vitro* to have direct anticancer action against the cancer-stricken host. Chimeric antigen receptor T (CAR-T) cells, TILs, and T cell receptor-engineered T cells are the three ACT types currently being researched for the treatment of cancer. CAR-T cell therapy entails

modifying T cells *in vitro* in an MHC-independent manner so that they can target tumor antigens and produce an anticancer immune response. With its tremendous effectiveness in treating leukemia, multiple myeloma, some forms of lymphoma, and mCRC, CAR-T cell therapy has a lot of room to grow[95]. Numerous clinical investigations on the safety and efficacy of CAR-T cell treatment are now being conducted in order to determine its therapeutic potential in the field of CRC. One of the first human trials using CAR-T cells to treat metastatic CRC was published by Hege *et al*[96]. It consisted of two phase I experiments with the same CART72 cells (C9701 and C9702). As first-generation CAR-T cells with a CD3-zeta intracellular signaling domain that specifically targeted the tumor-associated glycoprotein-72, CART72 cells were created. The way CART72 was administered in the two studies was different. In trial C9702, patients with CLM received direct hepatic artery infusions, whereas in trial C9701, CART72 was administered intravenously in increasing dosages. Despite a brief blood persistence and modest trafficking to tumor tissue, the data indicated a good safety profile. In addition, rapid clearance following CAR-T cell infusion was linked to CART72 immunogenicity.

Guanylylcyclase2C (GUCY2C) was mentioned by Magee *et al*[97,98] as a potential CAR-T cell target. In a mouse model lacking autoimmunity, they demonstrated that GUCY2C CAR-T cells may cure parenchymal CRC metastases. Additionally, they showed that GUCY2C targeted CAR-T cell treatment works well against metastatic cancers in mouse models and in human CRC xenograft models. Zhang *et al*[99] conducted a phase I study using CEA-positive CRC patients to create and assess CEA CAR-T cell treatment in 10 resistant and relapsed CRC patients with metastases. CAR-T cells were administered at five increasing dosage levels (1×10^5 to 1×10^8/CAR+/kg cells) to these individuals. The findings demonstrated that there were no significant side effects of CAR-T treatment. Seven of the ten patients—those with progressing illness throughout prior therapies—had stable disease following CAR-T cells therapy. Two patients had tumors removed, and two others had stable illnesses for more than 30 wk. They concluded that CEA CAR-T cell treatment, even at large dosages, was well tolerated in CEA+ CRC patients and that the majority of the treated patients showed some effectiveness.

Several ongoing trials are investigating the use of CAR-T cell in the treatment of CRC[100]. These included the safety, cellular kinetics, and efficacy of CYAD-101, an allogenic CAR-T cell therapy targeting ligands of NKG2D that was administered concurrently with FOLFOX, the efficiency and safety of NKR-2 CAR-T cells, EGFR and EGFR IL 12 CAR-T cell safety and feasibility, the use of anti-carcinoembryonic antigen targeted CAR-T cells, and investigating the efficacy and safety of HER2 chimeric antigen receptor-modified adenovirus-specific cytotoxic T lymphocytes administered in association with intratumoral injection of CAdVEC in patients with unresectable mCRC.

CONCLUSION

With the discovery and comprehension of several molecular and anatomical indicators, the landscape of systemic therapy for mCRC has significantly changed. To find the most effective treatment solution for mCRC patients, a baseline, thorough molecular study is now required. The effect of RAS, BRAF, HER2, POLE, MMR, MSS, and MSI status on therapy choice is summarized in this article. The selection of an efficient first-line therapy, which should consider both clinical factors and molecular signs, is crucial for deciding treatment outcomes. The second-line regimen is chosen based on the systemic therapies utilized in the first. For patients with RAS WT, third-line treatment, which includes EGFR inhibitors, should consider molecular profiling. Immunotherapy with pembrolizumab or nivolumab plus ipilimumab may be an option for patients with high microsatellite instability diseases.

The TME has been identified as a crucial player in CRC tumor growth and metastasis. This process involves all of the components from both bacteria and the host. Although each component has a unique function in CRC growth and metastasis, the majority of them act as a double-edged sword, promoting or inhibiting tumor expansion depending on the setting. TME-modulating treatment methods are showing promise. Many researches have confirmed that altering the TME can result in greater anti-tumor actions. Clinical investigations have indicated that TME remodeling has a high potential for improving medication therapeutic efficacy. Furthermore, because tumors tend to

acquire resistance, monotherapy is frequently insufficient. Combining TME remodeling techniques with other potential therapies, such as targeted treatment and immunotherapy, is another component we need to investigate in the near future to reduce treatment resistance.

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