DOI: 10.53469/jcmp.2025.07(11).23

Advances in Targeted Therapy and Drugs for Advanced Colorectal Cancer

Chunting Luo[1], Peng Xu[2,*]

[1]The First Clinical School, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Department of Oncology, Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
Correspondence Author

Abstract: ***Colorectal cancer (CRC) is one of the common malignant tumors of the digestive tract. Traditional conventional treatments primarily include surgery, chemotherapy, and radiotherapy. However, for advanced colorectal cancer, treatment often relies on drug rechallenge. Research on targeted therapy mainly focuses on molecular targets that inhibit tumor growth and proliferation. Anti-epidermal growth factor receptor (EGFR) drugs and anti-vascular endothelial growth factor (VEGF) drugs are options for treating advanced CRC. Some targeted drugs are already in clinical use, while others are undergoing clinical trials. In recent years, with advancements in molecular technology, an increasing number of biomarkers have been discovered. Targeted therapy has achieved significant success in the treatment of advanced CRC, leading to improved prognosis and quality of life for patients. This article summarizes the targeted pathways and drugs applied in the clinical treatment of rectal cancer in recent years, providing a reference for the precision treatment of advanced colorectal cancer.***

Keywords: Colorectal Cancer, Targeted Therapy, Targeted Drugs, Targeted Therapy-Related Pathways.

1. Introduction

Global cancer statistics data from 2022 reported 19.96 million new cancer cases worldwide. There were 9.74 million global cancer deaths in 2022, with the incidence of Colorectal Cancer (CRC) ranking third among global malignant tumors (9.6%). CRC is the second leading cause of cancer deaths globally [1]. CRC is one of the most common digestive system malignancies in China, with both its incidence and mortality rates showing an upward trend. China's population base accounts for 18.3% of the world's population, yet in 2022, new cancer cases in China constituted 24.2% of the global total. CRC accounted for 10.7% of all malignant tumor incidences in China. There were 240,000 CRC death cases, accounting for 9.3% of all malignant tumor deaths. The national CRC incidence and mortality rates were 36.63/100,000 and 17.00/100,000, respectively, showing an overall increasing trend [2]. Colorectal cancer has become a hallmark cancer associated with human development [3,4]. Many patients initially present with varying degrees of metastasis; 25%–30% of patients are diagnosed with metastasis at the time of initial diagnosis, while 15%–20% develop metastasis during disease progression after diagnosis. CRC is a major global health challenge. Patients with metastatic colorectal cancer (mCRC) should be managed by a multidisciplinary team, and treatment modalities include surgical therapy, chemotherapy, and local radiotherapy. Chemotherapy is the primary choice for mCRC patients. Although effective, chemotherapy has numerous limitations, including drug resistance, significant adverse effects, and poor safety. Therefore, among various treatment options, targeted therapy offers potential advantages of low toxicity, high efficacy, and precision. Previous studies have demonstrated the effectiveness of targeted therapy in exerting anti-tumor effects and improving survival rates in mCRC patients.

2. Targeted Therapy-Related Pathways and Drugs

2.1 EGFR Pathway

The Epidermal Growth Factor Receptor (EGFR) family members all possess tyrosine kinase activity and are thus also known as receptor tyrosine kinases. The family has four members: ErbB1 (EGFR), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). These are receptors located on the cell membrane surface, responsible for extracellular, intracellular, and transmembrane domain functions. Upon binding to Epidermal Growth Factor (EGF) and Transforming Growth Factor-alpha (TGF-α), these receptors activate intracellular nuclear kinases and trigger downstream signaling pathways, thereby influencing cell proliferation, apoptosis, and peritumoral angiogenesis [5]. Drugs targeting the EGFR pathway include cetuximab and panitumumab. Cetuximab is an IgG1 monoclonal antibody that specifically binds to the extracellular domain of EGFR, effectively blocking EGFR signal transduction, thereby reducing tyrosine kinase activation and altering tumor growth and metastasis-related cellular functions, including cell proliferation, DNA replication, tumor angiogenesis, cell migration, and invasion. On February 13, 2004, the US Food and Drug Administration (FDA) approved cetuximab for the treatment of advanced metastatic colorectal cancer. Several domestic experimental studies have shown that anti-EGFR drugs are only significantly effective against tumors harboring the wild-type KRAS genotype [6]. A recent international randomized, open-label phase II trial (PanaMa, AIO KRK 0212) results showed that adding panitumumab to 5-fluorouracil and leucovorin significantly prolonged progression-free survival (PFS) in patients with RAS wild-type mCRC (8.8 months vs. 5.8 months, HR=0.73 [95% CI: 0.56–0.94], P=0.015) [7]. A large clinical trial (AIO KRK0212) involving 248 patients with wild-type metastatic CRC showed that the efficacy of panitumumab combined with chemotherapy (leucovorin + fluorouracil) was superior to chemotherapy alone (objective response rate: 40.8% vs 26.0%; progression-free survival: 8.8 months vs 5.7 months) [8,9]. TERAZAWA included 36 elderly CRC patients (all unsuitable for chemotherapy due to tolerance issues, including 8 with right-sided tumors and 28

with left-sided tumors) and administered first-line panitumumab monotherapy [10]. The results indicated that panitumumab monotherapy was more effective for left-sided CRC than for right-sided CRC, similar to cetuximab.

2.2 VEGF Pathway

The VEGF pathway is another common target in mCRC. VEGF is a growth factor that stimulates blood vessel formation. Angiogenesis in tumor cells plays a crucial role in tumor growth, invasion, and metastasis. Therefore, inhibiting tumor angiogenesis is another hotspot in anti-tumor drug research. Monoclonal antibodies targeting VEGF, such as bevacizumab and ramucirumab, and inhibitors targeting VEGF receptors, such as sorafenib, sunitinib, and fruquintinib have, gradually become the preferred choices for anti-angiogenic therapy. In 2004, the US FDA approved bevacizumab combined with chemotherapy as a first-line treatment for metastatic colorectal cancer. Bevacizumab was approved for marketing in China in 2010. One study evaluated the efficacy and safety of bevacizumab combined with TOMIRI (likely irinotecan-based regimen). The bevacizumab + TOMIRI group compared to the TOMIRI group showed overall response rates of 83.02% (44/53) and 54.72% (29/53), respectively, with statistically significant differences (both $p<0.05$). KPS scores were (78.01±0.79) and (70.69±0.72), respectively, and PFS was (11.26±1.43) months and (8.01±0.97) months, respectively, with statistically significant differences (both $p<0.05$). The total incidence of adverse drug reactions showed no statistically significant difference ($p>0.05$) [8]. A large-sample, randomized, open-label phase III clinical trial by HEINEMANN et al. involving 352 patients with KRAS wild-type metastatic CRC showed that in patients with left-sided tumors, the median overall survival in the cetuximab group was superior to that in the bevacizumab group, whereas in patients with right-sided tumors, the median overall survival and progression-free survival in the cetuximab group were lower than those in the bevacizumab group [11,12].

2.3 Mitogen-Activated Protein Kinase Pathway

The Mitogen-Activated Protein Kinase (MAPK) pathway, namely the RAS/RAF/MEK/ERK pathway, is a key signaling cascade regulating cell division, survival, and differentiation, located downstream of the EGFR pathway. The MAPK pathway is hyperactivated in various cancers. The RAS gene family includes KRAS, NRAS, and HRAS. The most common RAS mutation is KRAS G12C, which occurs in approximately 4% of CRC cases. KRAS G12C inhibitors can rapidly restore the KRAS protein to its inactive state bound to guanosine diphosphate (GDP), exerting anti-tumor effects. Currently, KRAS G12C inhibitors used clinically can irreversibly bind to the cysteine residue on the KRAS protein (located adjacent to the Switch-II pocket of the KRAS protein), thereby blocking the binding of KRAS protein to GTP and ensuring that KRAS remains persistently in the inactive GDP-bound state [13] Among these, targeted therapy for the KRAS G12C mutation has been a highlight in recent years. Drugs targeting the KRAS G12C mutation include sotorasib and adagrasib [14]. According to current research status domestically and internationally, the KRAS G12C mutation accounts for about 3% of all CRC patients, with a prognosis significantly worse than that of wild-type patients [15,16,17]. Patients with advanced CRC harboring the KRAS G12C mutation have worse PFS and OS in late-line treatment compared to non-G12C mutant patients [18]. An example is the small molecule KRAS G12C inhibitor AMG510 (sotorasib) [19]. Currently, several clinical trials are investigating its safety and efficacy as monotherapy or in combination in CRC. A phase I/II open-label randomized clinical trial explored the safety, pharmacodynamics, and efficacy of AMG510 in late-line treatment of advanced solid tumors. Phase I results found the most common adverse reactions were diarrhea, fatigue, and nausea, with no dose-limiting toxicities or treatment-related deaths reported. However, the efficacy of AMG510 in mCRC was significantly inferior to that in NSCLC [20]. Subsequently, a phase II single-arm trial failed to meet its preset endpoints [21]. Regarding safety, diarrhea was the most common adverse reaction, with only 2 patients experiencing serious adverse events (back pain and severe renal impairment). MEK1 and MEK2 are downstream kinases in the MAPK pathway and are key effectors of BRAF and RAS signaling. MEK inhibitors trametinib and cobimetinib have demonstrated clinical efficacy in treating BRAF-mutant melanoma. ERK1/2 are the terminal kinases in the MAPK cascade and have become therapeutic targets with the development of ERK inhibitors, which have the potential to overcome resistance to upstream inhibitors and are currently under investigation in clinical trials [22].

2.4 Human Epidermal Growth Factor Receptor 2 Pathway

Human Epidermal Growth Factor Receptor 2 (HER2) is a proto-oncogene associated with various malignant tumors. Approximately 10% of CRC patients exhibit HER2 overexpression, and it is an effective therapeutic target in cetuximab-resistant CRC [23-24]. Both tucatinib and trastuzumab have the ability to prevent the phosphorylation process of truncated HER2. Some studies have led to the approval of anti-HER2 targeted drugs by the US FDA for the treatment of mCRC with Receptor Tyrosine Kinase 2 amplification [25]. In the phase II MOUNTAINEER study, patients with HER2-positive, RAS wild-type mCRC who had progressed on or were intolerant to standard therapy and had not received prior anti-HER2 targeted therapy were treated with tucatinib combined with trastuzumab. The results showed that tucatinib plus trastuzumab was well-tolerated, and long-term follow-up demonstrated sustained efficacy, proving long-term clinical benefit for responders. This combination represents an important chemotherapy-sparing option for HER2-positive mCRC [25-26]. The MOUNTAINEER-03 phase III clinical study (NCT05253651) is currently ongoing, and the efficacy of tucatinib + trastuzumab combined with chemotherapy as first-line treatment for HER2-positive mCRC is highly anticipated. Another study evaluated the recommended dose of trastuzumab deruxtecan (T-DXd) in HER2-positive mCRC patients. The results indicated that 5.4 mg/kg is the optimal monotherapy dose for HER2-positive mCRC patients [27].

2.5 Other Targeted Pathways

The Wnt/β-catenin signaling pathway is one of the key

pathways in cancer, frequently aberrantly activated in CRC and associated with poor prognosis. Intervening in the Wnt/β-catenin signaling pathway can affect cancer cell proliferation and induce apoptosis. Porcupine is an O-acyltransferase that binds to Wnt proteins and mediates their palmitoylation, subsequently facilitating Wnt protein secretion. Porcupine inhibitors, such as LGK974 and ETC159, can block the secretion and activity of all Wnt ligands, thereby preventing the activation of Wnt/β-catenin signaling in cancer cells. Frizzled receptors are cell surface receptors for Wnt ligands. Antagonizing Frizzled receptors can inhibit Wnt signaling and prevent downstream pathway activation. Additionally, directly inhibiting β-catenin is a rational therapeutic approach; disrupting the interaction between β-catenin and its transcriptional activators or directly degrading β-catenin can suppress the expression of Wnt target genes. In recent years, some natural products inhibiting the Wnt/β-catenin signaling pathway also show promise in providing effective therapeutic clues or potential new drugs, such as periplocin, IMU1003, 4β-hydroxywithanolide E, and gentianol. Various Wnt pathway inhibitors are currently undergoing clinical evaluation, showing promise in patients with Wnt ligand-dependent malignancies. Fibroblast Growth Factor Receptor (FGFR) mutation rate in CRC is about 4%. FGFR mutations lead to increased cell proliferation, survival, and angiogenesis, thereby promoting tumor progression. Targeting FGFR mutations is also a focus of new therapy development [28]. Mismatch Repair Deficiency (MMR) leading to Transforming Growth Factor Beta Receptor 2 (TGFBR2) mutations is associated with the development of Microsatellite Instability (MSI) CRC. Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusions are relatively rare in CRC but are clinically significant, predominantly found in right-sided, MSI-High (MSI-H), and RAS/BRAF wild-type tumors. NTRK gene fusions lead to hyperactivation of downstream pathways. Larotrectinib effectively inhibits this process by blocking tyrosine kinases within the signal pathway. Clinical trial results showed a response rate of 94% in patients treated with larotrectinib, demonstrating its anti-tumor effect across various solid tumors harboring NTRK fusion mutations [29]. TP53 mutations are very common in CRC patients, with a mutation rate as high as 50%. 70% of sporadic CRC cases are caused by mutations in the Adenomatous Polyposis Coli (APC) gene [30]. A prospective study involving 458 colorectal cancer patients found that during follow-up, 167 patients died. Among the remaining patients, the median pathological tumor cell survival rate was significantly lower in TP53 wild-type patients than in TP53 mutant patients (30%–47%, $P<0.001$) [31]. Besides losing the normal biological functions of TP53, mutant TP53 can also acquire new oncogenic activities through Gain of Function (GOF), accelerating carcinogenesis and metastasis [32]. One study found that the anatomical location determines the impact of TP53 GOF mutations on the prognosis of mCRC patients. TP53 GOF mutations were significantly associated with poorer survival in left-sided mCRC patients but showed no significant correlation with prognosis in right-sided mCRC patients, and were considered an independent poor prognostic factor for left-sided mCRC [33]. Silent Information Regulator 1 (SIRT1) is an emerging therapeutic target in CRC and is currently under investigation. c-Met (MET protein) is often overexpressed in various advanced solid tumors, including mCRC. To date, no therapy targeting c-Met overexpression has been approved for mCRC. Currently, research on ABBV-400, an antibody-drug conjugate (ADC) consisting of the c-Met-targeting antibody telisotuzumab linked to a novel topoisomerase I inhibitor, combined with bevacizumab for treating mCRC is underway [34-35]. One studyfound that NAMPT protein expression levels were significantly upregulated in colorectal cancer tissues, consistent with analysis results from the TCGA database, suggesting that PROTAC molecular drugs targeting NAMPT hold therapeutic promise for colorectal cancer patients [36].

3. Conclusion

In recent years, research on targeted drugs has continuously achieved new progress. Although chemotherapy remains the cornerstone of first-line treatment for mCRC, the emergence of targeted therapy and immunotherapy is rapidly transforming personalized medicine from concept to practice, profoundly influencing the future landscape of oncology. With ongoing support from substantial clinical trial data, targeted and immunotherapies are gradually advancing from second- and third-line treatments to first-line, early-stage neoadjuvant, and adjuvant settings. Certainly, any development faces obstacles and challenges, ranging from technical limitations to biological complexity, and from economic constraints to ethical considerations. Each step forward is precious. For instance, resistance to targeted and immunotherapies significantly limits long-term patient benefit. Exploring resistance mechanisms is a current hotspot and challenge, and combination therapy may be a potential strategy to overcome resistance mechanisms. Furthermore, exploring new biomarkers will help more patients benefit. Future research should focus on more personalized precision treatment to improve the prognosis of mCRC patients. Avoiding surgery and preserving organs are goals for the mCRC population. Targeted therapy and immunotherapy offer hope to numerous mCRC patients.

References

[1] Wang P, Huang Q, Wang SD, et al. Interpretation of the key points of Global Cancer Statistics 2022 [J]. Chin J Clin Thorac Cardiovasc Surg, 2024, 31(07): 933-954.

[2] Anonymous. Colorectal cancer screening, early diagnosis and treatment plan (2024 edition) [J]. Clin Educ Gen Pract, 2024, 22(10): 868-869.

[3] Bray F. Transitions in human development and the global cancer burden [C]// World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer, 2014: 42-55.

[4] Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels of the human development index [J]. Int J Cancer, 2016, 139(11): 2436-2446.

[5] Dos Santos ME, Araújo MC, Da Silva CMFP. Overweight is the main behavioral risk factor associated with colorectal cancer mortality in the Brazilian population: an ecological analysis [J]. Sci Rep, 2024, 14: 13619.

[6] Yan JZ, Bian F, Ma G, et al. Progress in targeted drug therapy for colorectal cancer [J]. Clin Res, 2022, 30(02): 195-198.

[7] Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab [J]. J Clin Oncol, 2008, 26(3): 374-379.
[8] Stahler A, Karthaus M, Fruehauf S, et al. Panitumumab plus 5-fluorouracil and folinic acid or 5-fluorouracil and folinic acid alone as maintenance therapy in RAS wild-type metastatic colorectal cancer (PanaMa, AIO KRK 0212): final efficacy analysis of a randomised, open-label, phase 2 trial [J]. Clin Med, 2025, 79: 1030.
[9] Feng Y, Guo H, Zhao JB, et al. Clinical study of bevacizumab combined with TOMIRI chemotherapy in the treatment of patients with advanced colorectal cancer [J]. Chin J Clin Pharmacol, 2024, 40(15): 2170-2173.
[10] Modest DP, Karthaus M, Fruehauf S, et al. Panitumumab plus fluorouracil and folinic acid versus fluorouracil and folinic acid alone as maintenance therapy in RAS wild-type metastatic colorectal cancer: The randomized PANAMA trial (AIO KRK 0212) [J]. J Clin Oncol, 2022, 40(1): 72-82.
[11] Terazawa T, Kato T, Goto M, et al. Phase II study of panitumumab monotherapy in chemotherapy-naïve frail or elderly patients with unresectable RAS wildtype colorectal cancer: OGSG 1602 [J]. Oncologist, 2021, 26(1): e17-e47.
[12] Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab or bevacizumab for advanced colorectal cancer: final survival and per-protocol analysis of FIRE-3, a randomised clinical trial [J]. Br J Cancer, 2021, 124(3): 587-594.
[13] Huang C, Xiao ZX, Su BW, et al. Research progress on EGFR inhibitors combined with KRAS G12C inhibitors in the treatment of advanced colorectal cancer [J]. J Changchun Univ Chin Med, 2025, 41(04): 461-466.
[14] Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small cell lung cancer harboring a KRASG12C mutation [J]. N Engl J Med, 2022, 387(2): 120-131.
[15] Ou SI, Jänne PA, Leal TA, et al. First-in-human phase I/Ib dose-finding study of adagrasib (MRTX849) in patients with advanced KRASG12C solid tumors (KRYSTAL-1) [J]. J Clin Oncol, 2022, 40(23): 2530-2538.
[16] Zhang Y, Li X, Liu C, et al. 1786P Distribution of KRAS G12C somatic mutations in 41,913 Chinese cancer patients [J]. Ann Oncol, 2021, 32: S1220-S1221.
[17] Zhong J, Sun ZJ, Cao YP, et al. Research progress of KRAS G12C inhibitors and combination with EGFR inhibitors in the treatment of advanced colorectal cancer [J]. Chin J Surg Oncol, 2023, 15(01): 98-104.
[18] Fakih M, Tu H, Hsu H, et al. Real-world study of characteristics and treatment outcomes among patients with KRAS p.G12C-mutated or other KRAS mutated metastatic colorectal cancer [J]. Oncologist, 2022, 27(8): 663-674.
[19] Canon J, Rex K, Saiki AY, et al. The clinical KRASG12C inhibitor AMG 510 drives anti-tumour immunity [J]. Nature, 2019, 575(7781): 217-223.
[20] Hong DS, Fakih MG, Strickler JH, et al. KRASG12C inhibition with sotorasib in advanced solid tumors [J]. N Engl J Med, 2020, 383(13): 1207-1217.
[21] Fakih MG, Kopetz S, Kuboki Y, et al. Sotorasib for previously treated colorectal cancers with KRASG12C mutation (CodeBreak100): a prespecified analysis of a single-arm, phase 2 trial [J]. Lancet Oncol, 2022, 23(1): 115-124.
[22] Ou SI, Jänne PA, Leal TA, et al. First-in-human phase I/Ib dose-finding study of adagrasib (MRTX849) in patients with advanced KRASG12C solid tumors (KRYSTAL-1) [J]. J Clin Oncol, 2022, 40(23): 2530-2538.
[23] Canon J, Rex K, Saiki AY, et al. The clinical KRASG12C inhibitor AMG 510 drives anti-tumour immunity [J]. Nature, 2019, 575(7781): 217-223.
[24] Zhang XL, Zhou JW. Research progress in third-line targeted and immunotherapy for advanced colorectal cancer [J]. J Henan Univ (Med Sci), 2022, 41(06): 391-399.
[25] Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study [J]. Lancet Oncol, 2023, 24(5): 496-508.
[26] Yang DY, Ma D. Advances in the treatment of advanced colorectal cancer in 2024 [J]. J Evid Based Med, 2024, 24(06): 346-348.
[27] Raghav K, Siena S, Takashima A, et al. Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): primary results from a multicentre, randomised, phase 2 trial [J]. Lancet Oncol, 2024, 25(9): 1147-1162.
[28] Facchinetti F, Hollebecque A, Bahleda R, et al. Facts and new hopes on selective FGFR inhibitors in solid tumors [J]. Clin Cancer Res, 2020, 26(4): 764-774.
[29] Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials [J]. Lancet Oncol, 2020, 21(4): 531-540.
[30] Dong W, Lu J, Li Y, et al. SIRT1: a novel regulator in colorectal cancer [J]. Biomed Pharmacother, 2024, 178: 117176.
[31] Maki H, Haddad A, Ayabe RI, et al. TP53 alteration and its effect on pathologic response are associated with survival after resection of colorectal liver metastases [J]. J Gastrointest Surg, 2023, 27: 2597-2600.
[32] Roszkowska KA, Piecuch A, Sady M, et al. Gain of function (GOF) mutant p53 in cancer-current t herapeutic approaches [J]. Int J Mol Sci, 2022, 23: 10917.
[33] Kajiwara T, Nishina T, Yamashita R, et al. Sidedness-dependent prognostic impact of gene alterations in metastatic colorectal cancer in the nationwide cancer genome screening project in Japan (SCRUM-Japan GI-SCREEN) [J]. Cancers (Basel), 2023, 15: 2351.
[34] Sharma M, Strickler JH, Sommerhalder D, et al. First-in-human study of ABBV-400, a novel c-Met-targeting antibody-drug conjugate, in advanced solid tumors: results in colorectal cancer [J]. J Clin Oncol, 2024, 42(16_suppl): 3515.
[35] Liu XC, Cao LX. Impact of KRAS/TP53 co-mutation on efficacy and prognosis in patients with colorectal cancer [J]. Chin J Diagn Pathol, 2025, 32(07): 894-899.
[36] Liu SL, Yao X, Liu JC, et al. Therapeutic efficacy of targeted NAMPT small molecule drugs in NAPRT-low

expressing colorectal cancer [J]. Tumor, 2024, 44(10): 979-992.