中国临床研究 Chin J Clin Res, September 2024, Vol.37, No.9
Cite as: Chen YX, Lei XF, Zhang M, Chen Q, Chen HX. Research progress of regorafenib in the treatment of colorectal cancer [J]. Chin J Clin Res, 2024, 37(9):1319-1322.
DOI: 10.13429/j.cnki.cjcr.2024.09.002

Research progress of regorafenib in the treatment of colorectal cancer

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Abstract: Colorectal cancer (CRC)is a common malignant tumor of digestive tract with an increasing incidence and mortality worldwide, and most patients have lost the opportunity of surgical treatment once diagnosed. With the continuous development of precision targeted therapy, anti-angiogenesis targeted drugs have achieved good therapeutic effect in the treatment of advanced CRC. Regorafenib is a multi-target oral tyrosine kinase inhibitor, which can improve the tumor immune microenvironment by regulating tumor-associated macrophage, vascular endothelial growth factor receptor, and has a synergistic effect with immunotherapy. This article reviews the progress of basic and clinical research on regorafenib in the field of CRC.

Keywords: Colorectal cancer; Regorafenib; Vascular endothelial growth factor receptors; Targeted drug; Tumor-associated macrophages

In recent years, the incidence and mortality rates of colorectal cancer (CRC) in China have been on the rise. The *China Cancer Statistics Report 2020* indicated that CRC ranked 2nd and 5th among all malignant tumors in terms of incidence and mortality, respectively [1]. Chemotherapy remains the cornerstone of CRC treatment, but advancements in science and technology have introduced new targeted and immunotherapeutic agents, providing patients with more treatment options.

Since its clinical introduction in 2018, regorafenib has become a standard recommendation for third-line treatment of CRC. It is used for patients who have previously been treated with fluoropyrimidine-based therapy and who have received anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) therapy for wild-type metastatic CRC. Regorafenib is a novel oral multi-kinase inhibitor that plays a significant role in effectively blocking the activity of various protein kinases, including inhibition of tumor VEGF receptors (VEGFR) 1 and VEGFR3, fibroblast growth factor receptor 1, mutated oncogenic kinases such as tyrosine kinase receptor (KIT), rearranged during transfection (RET), and B-Raf proto-oncogene, serine/threonine kinase (BRAF) as well as platelet-derived growth factor receptor-β (PDGFR-β) [2-3]. This paper will review the research progress on regorafenib in the treatment of CRC.

1 Development of Regorafenib in Clinical Application

1.1 Animal Studies on Regorafenib

Wilhelm *et al.* [2] found through *in vitro* studies that regorafenib effectively inhibits angiogenesis and stromal receptor tyrosine kinases (RTKs), including VEGFR1, VEGFR2, VEGFR3, tyrosine kinase receptor 2 (TIE2), and PDGFR-β. These signals promote tumor angiogenesis, vessel stability, and lymphangiogenesis, playing crucial roles in the tumor microenvironment and contributing to tumor development and metastasis. Combined blockade of VEGFR2 and TIE2 signaling by regorafenib might produce more profound anti-angiogenic effects than inhibiting VEGF signaling alone. Regorafenib also showed effective inhibition of oncogenic RTKs KIT^{K642E} and RET^{C634W} (20-40 nmol/L), suggesting potential clinical benefit in *RET*-mutant-driven tumors, which occur in a subset of medullary thyroid carcinomas or gastrointestinal stromal tumors (GISTs) with *KIT* mutations. Regorafenib effectively inhibits the serine/threonine kinase BRAF (a downstream target in the RAS signaling pathway) and its oncogenic mutant $B\text{-}RAF^{V600E}$, and its anti-tumor efficacy can be enhanced in combination with MEK or PI3K inhibitors. These results indicate that regorafenib effectively inhibits key angiogenic and tumorigenic kinases driving various human cancers and has demonstrated efficacy in preclinical models by blocking the growth of multiple human tumor xenografts, suggesting potential effectiveness in humans.

1.2 Phase Ⅰ Clinical Trials of Regorafenib for CRC

Mross and Strumberg et al. [4-5] reported that in Phase Ⅰ clinical trials, 66% of patients treated with regorafenib had controlled disease (partial response or stable disease). In an extended Phase Ⅰ cohort study of metastatic CRC patients, regorafenib showed anti-tumor efficacy and manageable adverse effects. Regorafenib, as a multi-kinase inhibitor, demonstrated acceptable safety and preliminary evidence of anti-tumor activity.

1.3 Phase Ⅱ Clinical Trials of Regorafenib for CRC

Cardone et al. [6] reported the results of the

STREAM study, a Phase Ⅱ academic, multicenter, single-arm trial using regorafenib to treat RAS-mutant metastatic CRC. The study assessed efficacy based on the proportion of patients without progression 6 months after enrollment (6-month progressive-free survival, 6mo-PFS), with patients pre-treated with fluoropyrimidine, oxaliplatin, and bevacizumab. Results showed 8/22 patients had 6mo-PFS in the first phase, with a total of 14 out of 46 patients. The objective response rate (ORR) was 10.9%, the disease control rate (DCR) was 54.6%, the median progression-free survival (mPFS) was 3.6 months, and the median overall survival (mOS) was 18.9 months, with mPFS2 (from study entry to subsequent-line treatment progression) at 13.3 months. 39.1% of patients experienced ≥3 grade events, mostly hand-foot syndrome (13%), fatigue, and hyperbilirubinemia (6.5%). In multivariate analysis, baseline metabolic assessment correlated with OS, while early metabolic response was not associated with clinical outcomes. Bekaii-Saab et al. [7] also conducted the ReDOS study to evaluate dose escalation and preventive local hormone strategies with regorafenib in recurrent metastatic CRC patients. Patients were randomly assigned to either an 80 mg/d group (with weekly escalation to 160 mg/d) or a 160 mg/d group, and further randomized 1:1:1:1 to preventive local hormone use for 12 weeks or based on drug response. The study endpoint was to compare the proportion of patients starting the third cycle of regorafenib treatment between groups. Results showed that 43% of the 80 mg/d group started the third cycle, compared to 25% of the 160 mg/d group. The 80 mg/d starting dose with weekly escalation showed a clear improvement in mOS and potentially reduced the incidence of hand-foot syndrome with preventive local hormone use.

1.4 Phase Ⅱ Clinical Trials of Regorafenib for CRC

Grothey et al. [3] conducted the CORRECT study, an international, multicenter, placebo-controlled Phase Ⅱ trial, enrolling 760 patients randomized in a 2:1 ratio to regorafenib (n=505) or placebo (n=255) groups, all of whom had prior anti-VEGF treatment. Results showed regorafenib significantly extended the mOS to 6.4 months, reducing the risk of death by 23%. Safety analysis revealed that severe adverse event (AE) rates were 93% in the regorafenib group versus 61% in the placebo group, with common AEs including hand-foot skin reactions, fatigue, diarrhea, hypertension, and rash or desquamation, which were generally manageable and had similar impacts on quality of life compared to placebo. This result globally confirmed that regorafenib can improve survival in mCRC patients after standard treatment failure. Additionally, a randomized, double-blind, placebo-controlled, parallel-group Phase Ⅲ trial (CONCUR study) conducted at 25 hospitals after CORRECT included 243 metastatic CRC patients, randomized in a 2:1 ratio to regorafenib (204 patients) or placebo (68 patients). The baseline characteristics of both groups were balanced and comparable. Results further confirmed regorafenib's efficacy: compared to placebo (mOS: 6.3 months), regorafenib significantly extended mOS to 8.8 months and reduced the risk of death by 45%. The mPFS for regorafenib and placebo groups was 3.2 months and 1.7 months, respectively. Subgroup analysis indicated that patients with no prior anti-VEGF or anti-EGFR treatment had a hazard ratio of 0.31 (95% CI: 0.19-0.53), whereas those with prior targeted anti-tumor treatments (anti-VEGF, anti-EGFR, or both) had a hazard ratio of 0.78 (95% CI: 0.51-1.19). Data comparison showed that mOS was longer in the regorafenib group in the CONCUR study compared to the CORRECT study, suggesting that mCRC patients might benefit more from regorafenib treatment, possibly due to a lower proportion of patients with prior targeted therapy in CONCUR. Additionally, Van Cutsem et al. [9] confirmed the safety of regorafenib through a large Phase Ⅱb study (CONSIGN).

2 Regorafenib Combined with Other Treatments

2.1 Regorafenib Combined with Immunotherapy

Immune checkpoint inhibitors (ICIs) are gaining increasing attention in CRC treatment, particularly for cancers with deficient mismatch repair (MMR) which have a high number of somatic mutations. A proof-of-concept study found that MMR-deficient CRCs are sensitive to immune checkpoint blockade with PD-1 antibodies. Several studies indicate that regorafenib combined with ICIs can effectively inhibit tumor cell growth and reduce the infiltration of immunosuppressive macrophages, showing efficacy in advanced CRC. The REGONIVO study presented at the 2019 ASCO Annual Meeting showed that for microsatellite stable (MSS) metastatic CRC, regorafenib combined with the ICI nivolumab had an ORR of over 30%, and this benefit was successfully translated into progression-free survival (PFS) and overall survival (OS) benefits in subsequent follow-ups. This suggests that regorafenib combined with immunotherapy could potentially improve the survival of MSS metastatic CRC patients in third-line treatment. Building on REGONIVO, Fakih et al. assessed the efficacy of regorafenib combined with CTLA-4 inhibitors in MSS metastatic CRC, using the RIN regimen (regorafenib + ipilimumab + nivolumab). Results showed an ORR of 27.6% in CRC patients failing standard treatments, with better outcomes in non-liver metastatic patients, representing a significant improvement over traditional third-line treatments. Professor Xu Ruihua's team at Sun Yat-sen University conducted the REGOTORI trial, which predicted the efficacy of regorafenib combined with toripalimab in MSS metastatic CRC. The study showed an ORR of

15.2%, DCR of 36.4%, mPFS of 2.1 months, and mOS of 15.5 months, with a higher ORR in non-liver metastatic CRC (30% vs. 8.7%). The study also suggests that baseline gut microbiota may become a marker for survival benefit in metastatic CRC patients. This provides strong evidence for the benefit of regorafenib combined with PD-1 monoclonal antibodies in treating CRC patients. In the future, regorafenib, as a small-molecule targeted drug, combined with immunotherapy may achieve further breakthroughs in improving objective response rates in CRC patients.

2.2 Regorafenib Combined with Chemotherapy

Fluoropyrimidine-based therapy is the cornerstone of CRC chemotherapy, and chemotherapy is a common method for treating metastatic CRC. However, many studies show that chemotherapy has strong toxic reactions, which reduce patient tolerance and lead to poor compliance. Regorafenib helps combat multi-drug resistance (MDR) in colorectal cancer, thereby improving chemotherapy efficacy. Recent studies have shown that regorafenib combined with chemotherapy is effective, significantly inhibiting tumor angiogenesis, improving tumor cell immune evasion and inflammatory damage indicators, reducing tumor marker levels, and enhancing quality of life with high safety. REGTAS, a multicenter, single-arm Phase Ⅱ study, explored the efficacy of regorafenib combined with TAS-102 for treating refractory mCRC. The study included 21 mCRC patients from five centers who failed standard treatments, with regorafenib administered at 120 mg/d for 21 days in a 4-week cycle (or an initial dose of 80 mg/d, increasing weekly by 40 mg to 120 mg/d); TAS-102 was given biweekly (30 mg/m2 twice daily, days 1-5). Results showed that among 19 patients evaluable for efficacy, the overall PFS was 4.3 months, OS was 12.7 months, and DCR was 78.9%. The liver metastasis subgroup had a PFS of 4.3 months, OS of 11.8 months, and DCR of 80.0%, similar to the overall population, with good safety.

2.3 Regorafenib Combined with Radiotherapy

There is limited research on regorafenib combined with radiotherapy for CRC, but some studies have shown that this combination can control tumors in certain patients. However, this treatment may not be effective for all patients and may bring side effects such as fatigue, skin reactions, and oral ulcers. Therefore, when using regorafenib combined with radiotherapy, a personalized treatment plan should be considered, taking into account the patient's condition, treatment goals, and potential side effects. Studies comparing regorafenib combined with radiotherapy and immunotherapy against regorafenib alone for metastatic CRC patients are also ongoing.

3 Conclusion

The clinical application of regorafenib provides a broader range of treatment options for advanced CRC patients. From a comprehensive tumor management perspective, it may be considered for earlier use in second-line treatment to offer more survival benefits. The prevention and treatment of CRC remain urgent issues, and regorafenib has been shown to normalize blood vessels and improve the tumor microenvironment, thus enhancing its synergistic anti-tumor effects with ICIs. Consequently, combined regorafenib and immunotherapy is highly anticipated in clinical settings. Additionally, other targeted and immunotherapy combinations are still being explored to identify effective strategies for improving the immune microenvironment of MSS metastatic CRC. Future research should delve deeper into the combined mechanisms of different drugs through basic and translational studies and conduct large-scale clinical trials to improve survival benefits for this patient population. However, due to the limitations of clinical trials, the long-term efficacy and safety of regorafenib need further observation and research. Moreover, the applicability and dose adjustments for different patient groups require more practice and research. Overall, regorafenib shows promise but needs further evaluation and optimization in broader clinical practice.

Conflicts of Interest: None

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Submission received: 2023-11-30 / **Revised:**2024-03-04

· 研究进展 ·

瑞戈非尼治疗结直肠癌的研究进展

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摘要：结直肠癌（CRC）是一种常见的消化道恶性肿瘤，其发病率和死亡率在全球范围内呈上升趋势，大多数患者一经确诊已失去手术治疗的机会。随着精准靶向治疗的不断发展，抗血管生成靶向药物在治疗晚期 CRC 方面取得了较好的治疗效果。瑞戈非尼是一种多靶点口服酪氨酸激酶抑制剂，它可以通过调节肿瘤相关巨噬细胞、血管内皮生长因子受体（VEGFR），改善肿瘤免疫微环境，并与免疫治疗产生协同作用。本文综述瑞戈非尼在 CRC 领域相关基础和临床研究的进展。

关键词：结直肠癌；瑞戈非尼；血管内皮生长因子受体；靶向药物；肿瘤相关巨噬细胞
中图分类号：R735.3　R730.51　**文献标识码**：A　**文章编号**：1674-8182(2024)09-1319-04

Research progress of regorafenib in the treatment of colorectal cancer

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Abstract: Colorectal cancer (CRC) is a common malignant tumor of digestive tract with an increasing incidence and mortality worldwide, and most patients have lost the opportunity of surgical treatment once diagnosed. With the continuous development of precision targeted therapy, anti-angiogenesis targeted drugs have achieved good therapeutic effect in the treatment of advanced CRC. Regorafenib is a multi-target oral tyrosine kinase inhibitor, which can improve the tumor immune microenvironment by regulating tumor-associated macrophage, vascular endothelial growth factor receptor, and has a synergistic effect with immunotherapy. This article reviews the progress of basic and clinical research on regorafenib in the field of CRC.

Keywords: Colorectal cancer; Regorafenib; Vascular endothelial growth factor receptors; Targeted drug; Tumor-associated macrophages

近些年来，我国结直肠癌（colorectal cancer, CRC）的发病率和死亡率均呈现上升趋势。2020 年中国癌症统计报告显示，我国 CRC 发病率、死亡率在全部恶性肿瘤中分别位居第 2 和第 5 位[1]。化疗是 CRC 治疗的基石，但随着科学技术的深入发展，新型靶向药物、免疫药物的问世为患者带来了更多的治疗选择。

自 2018 年起，瑞戈非尼进入临床以来，已成为 CRC 三线治疗的标准推荐，可用于治疗曾接受过以氟尿嘧啶为基础治疗，及既往接受过抗血管内皮生长因子（vascular endothelial growth factor, VEGF）治疗、抗表皮生长因子受体（epidermal growth factor receptor, EGFR）治疗野生型的转移性 CRC 患者。瑞戈非尼是一种新型口服多激酶抑制剂，在有效阻断多种蛋白激酶的活性方面起着重要作用，包括抑制肿瘤 VEGF 受体（VEGF receptor, VEGFR）1 和 3，成纤维细胞生长因子受体 1、突变的致癌激酶[如酪氨酸激酶受体（tyrosine kinase receptor, KIT）、转染期间重排（rearranged during tranfection, RET）和 B-Raf 原癌基因丝氨酸/苏氨酸蛋白激酶（B-Raf proto-oncogene, serine/threonine kinase, BRAF）]以及血小板源性生长因子受体 β（platelet derived growth factor receptor, PDGFR-β）等[2-3]。本文将对瑞戈非尼治疗 CRC 的研究进展进行综述。

1　瑞戈非尼在临床应用的发展

1.1　*瑞戈非尼的动物实验*　Wilhelm 等[2]通过体外研究发现瑞戈非尼能有效抑制促血管生成和间质受体酪氨酸激酶（receptor tyrosine kinase, RTK）、VEGFR1、VEGFR2、VEGFR3、上皮生长因子样域酪氨酸激酶 2（tunica interna endothelial cell kinase 2, TIE2）和 PDGFR-β，这些信号促进肿瘤新生血管形成、血管稳定和淋巴管形成，在肿瘤微环境中发挥重要作用，并促成肿瘤发展和转移的形成。瑞戈非尼联合阻断 VEGFR2 和 TIE2 信号可能比单独抑制 VEGF 信号产生更深远的抗血管增生作用。瑞戈非尼还显示出对体外致癌 RTKs KIT^{K642E} 和

DOI：10.13429/j.cnki.cjcr.2024.09.002
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出版日期：2024-09-20

QR code for English version

RET^{C634W}的有效抑制(20～40 nmol/L)[2],这表明瑞戈非尼可能在由 *RET* 突变驱动的肿瘤类型中具有临床潜力,*RET* 突变发生在甲状腺髓样肿瘤的一个子集中,或胃肠道间质瘤(gastrointestinal stromal tumor, GIST)中 *KIT* 突变。瑞戈非尼能有效抑制 BRAF(RAS 信号通路的下游靶点)及其致癌突变体 $B\text{-}RAF^{V600E}$,瑞戈非尼与 MEK 或 PI3K 抑制剂合用可增强瑞戈非尼的抗肿瘤疗效。这些结果表明瑞戈非尼有效地抑制了许多驱动多种人类肿瘤的关键血管生成和肿瘤生成激酶,并在临床前模型中有效地阻止了大量人类肿瘤异种移植的生长,提示瑞戈非尼可能对人类也有效。

1.2　*瑞戈非尼单药治疗 CRC 的Ⅰ期临床试验*　Mross 和 Strumberg 等[4-5]报道了在Ⅰ期临床试验中,66%接受瑞戈非尼治疗的患者病情得到控制(部分缓解或病情稳定),在转移性 CRC 患者的Ⅰ期扩展队列研究中,瑞戈非尼显示出抗肿瘤疗效和可控的不良反应,多激酶抑制剂瑞戈非尼显示出可接受的安全性,并且初步证据表明其具有抗肿瘤活性。

1.3　*瑞戈非尼单药治疗 CRC 的Ⅱ期临床试验*　Cardone 等[6]报告了 STREAM 研究,即使用瑞戈非尼治疗 *RAS* 突变型转移性 CRC 的一项学术、多中心、单臂Ⅱ期试验的研究结果。该研究根据研究入组 6 个月后无进展的患者比例(6 months-progressive free survival, 6mo-PFS)来评估疗效,入组患者接受氟尿嘧啶、奥沙利铂和贝伐珠单抗预治疗。结果显示第一阶段 6mo-PFS 的患者数为 8/22,在 46 例总体人群中为 14 例。客观缓解率(objective response rate, ORR)为 10.9%,疾病控制率(disease control rate, DCR)为 54.6%,中位无进展生存期(median progressive free survival, mPFS)为 3.6 个月,中位总生存期(median overall survival, mOS)为 18.9 个月,mPFS2(从进入研究至后线治疗进展)为 13.3 个月。39.1%的患者发生 3 级及以上不良事件,其中大部分为手足综合征(12.8%)、疲劳(6.4%)和高胆红素血症(6.4%)。在多变量分析中,基线代谢评估与 OS 相关,而早期代谢反应与临床结局无关。

Bekaii-Saab 等[7]也开展了 ReDOS 研究,该研究用于评估在复发转移性 CRC 患者中瑞戈非尼剂量递增和预防性局部使用激素策略,该试验根据瑞戈非尼起始量将患者随机分为 80 mg/d 的 A 组(每周剂量递增至 160 mg/d)和 160 mg/d 的 B 组,并根据是否局部使用激素处理,按 1∶1∶1∶1 将患者随机分为预防性使用激素 12 周的 A1、B1 组,及根据药物反应局部使用激素的 A2、B2 组,研究终点为比较 A 组(A1+A2)和 B 组(B1+B2)中开始第 3 周期瑞戈非尼治疗的比例,结果显示,A 组开始第 3 周期治疗的比例为 43%,而 B 组仅为 25%,A 组中位 OS 有明显改善,表明瑞戈非尼起始 80 mg/d,每周递增至 160 mg/d 的策略优于起始剂量即为 160 mg/d 的剂量,同时,预防性局部使用可能会降低手足综合征的发生率。

1.4　*瑞戈非尼单药治疗 CRC 的Ⅱ期临床试验*　Grothey 等[3]进行了 CORRECT 研究,该研究为一项国际、多中心、安慰剂对照的Ⅱ期临床试验,将纳入的 760 例患者以 2∶1 比例随机入组瑞戈非尼组(n=505)和安慰剂组(n=255),患者均接受过既往抗 VEGF 治疗。其结果显示,瑞戈非尼使患者的 mOS 显著延长至 6.4 个月,降低 23%的死亡风险。安全性分析显示,瑞戈非尼组与安慰剂组严重不良事件发生率分别为 93%和 61%,常见不良事件包括手足皮肤反应、疲劳、腹泻、高血压和皮疹或脱屑,但通常可控、可预测,对患者生活质量的影响与安慰剂近似。这一结果在全球范围内首次证实,瑞戈非尼可使标准治疗失败后的 mCRC 患者获得生存改善。

此外,一项继 CORRECT 研究之后在中国(含香港、台湾地区)、韩国和越南的 25 家医院开展的随机、双盲、安慰剂对照、平行组、Ⅲ期临床试验(CONCUR 研究)[8],一共纳入 243 例转移性 CRC 患者,按 2∶1 比例将患者随机分组,给予瑞戈非尼(204 例)或安慰剂(68 例)治疗,两组患者的基线特征均衡可比。其结果进一步证实了瑞戈非尼的确切疗效,相比于安慰剂(mOS:6.3 个月),瑞戈非尼显著延长患者的 mOS 至8.8 个月,并降低 45%的死亡风险。瑞戈非尼组与安慰剂组的 mPFS 分别为 3.2 个月和 1.7 个月。亚组分析表明,既往均未接受过抗 VEGF 或抗 EGFR 治疗的患者其评估风险比为 0.31 (95%*CI*:0.19～0.53),既往接受过任意靶向抗肿瘤治疗(抗 VEGF,抗 EGFR,或两者皆有)的患者其评估风险为 0.78(95%*CI*:0.51～1.19)。若做单纯的数据对比,CONCUR 研究中瑞戈非尼组患者的 mOS 较 CORRECT 研究更长,提示亚洲及中国 mCRC 患者可能从瑞戈非尼治疗中获益更多,这可能与 CONCUR 中接受既往靶向治疗的患者比例更低有关。同时,Van Cutsem 等[9]通过大型Ⅱb 研究(CONSIGN)也证实了瑞戈非尼的安全性。

2　瑞戈非尼联合其他治疗

2.1　*瑞戈非尼联合免疫治疗*　免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)在 CRC 治疗中越来越受到重视,缺乏错配修复(mismatch repair,MMR)的癌症基因组包含异常高数量的体细胞突变[10]。在一项概念验证研究中,发现 MMR 缺陷的 CRC 对抗 PD-1 抗体的免疫检查点阻断敏感[11-12]。

多项研究表明,瑞戈非尼联合 ICIs 在抑制肿瘤细胞生长、减少免疫抑制性巨噬细胞的浸润方面有一定作用,对晚期 CRC 疗效确切[13-18]。在 2019 年的 ASCO 年会上,日本的 REGONIVO 研究显示,对于微卫星稳定(microsatellite stability, MSS)的转移性 CRC,瑞戈非尼联合免疫检查点抑制剂纳武利尤单抗的 ORR 超过 30%,并且 ORR 获益在后续随访中也成功地转化无进展生存期和总生存期的获益[14],表明瑞戈非尼联合免疫治疗有可能改善 MSS 转移性 CRC 患者三线治疗的生存现状。Fakih 等[19]在 REGONIVO 研究基础上联合细胞毒性 T 淋巴细胞相关蛋白 4(cytotoxic T-lymphocyte antigen 4, CTLA-4)抑制剂双免联合靶向治疗评估对 MSS 转移性 CRC 的疗效,即瑞戈非尼+伊匹木单抗+纳武利尤单抗(RIN 方案)用于治疗 MSS 转移性 CRC 患者,结果表明标准治疗失败的 CRC 患者中 ORR 达 27.6%,其中非肝转移人群中获益更佳,对比转移性 CRC 传统的三线治疗有了显著的提升。

中山大学徐瑞华教授团队同期开展了首个针对中国人群的 REGOTORI 临床试验[15],该研究在于预测瑞戈非尼联合特

瑞普利单抗治疗 MSS 型转移性 CRC 的疗效,结果显示在可评估的 33 例患者中,ORR 为 15.2%、DCR 为 36.4%,mPFS 为 2.1 个月,mOS 为 15.5 个月,在无肝脏转移的转移性 CRC 中 ORR 更高(30.0% *vs* 8.7%)。同时也表明基线肠道微生物菌群中梭杆菌属有望成为转移性 CRC 患者的生存获益标志,该研究为瑞戈非尼联合 PD-1 单抗在治疗 CRC 患者中获益提供了更有力的证据。

未来,瑞戈非尼这类小分子靶向药物联合免疫治疗方式有可能在改善 CRC 患者客观缓解率方面取得更多突破。

2.2　瑞戈非尼联合化疗　氟尿嘧啶是 CRC 化学治疗的基石,化疗是临床上治疗转移性 CRC 的常用手段,然而,许多研究表明,化疗具有较强毒性反应,降低患者耐受性从而导致依从性不佳[20-22]。瑞戈非尼有利于抗结肠癌多药耐药(multi-drug resistance, MDR),从而提高化疗疗效。近些年来的研究表明[23-25],瑞戈非尼联合化疗治疗结直肠癌效果显著,可有效抑制肿瘤血管新生,改善肿瘤细胞免疫逃逸、炎症损伤指标水平,从而使肿瘤标志物水平降低,提高生存质量,且安全性高。REGTAS[26]是一项多中心单臂Ⅱ期研究,以探索瑞戈非尼联合曲氟尿苷替匹嘧啶(TAS-102)治疗难治性 mCRC 的疗效。纳入了 5 个中心 21 例标准治疗失败的 mCRC 患者,瑞戈非尼 120 mg/d 给药,持续 21 天,以 4 周为一周期(或起始剂量 80 mg/d,随后每周增加 40 mg 至 120 mg/d);TAS-102 每两周给药一次(30 mg/m^{2}每天两次,第 1~5 天)。结果显示:在可进行疗效评估的 19 例患者中,整体人群的 PFS 达 4.3 个月,OS 达12.7个月,DCR 达 78.9%。其中肝转移亚组的 PFS 达 4.3 个月,OS 达 11.8 个月,DCR 达 80.0%,和整体人群的疗效相近、安全性好。

2.3　瑞戈非尼联合放疗　瑞戈非尼联合放疗治疗 CRC 研究较少,在部分研究中,一些患者对这种联合治疗产生了反应,其肿瘤得到了控制[27]。但是,这种治疗方法并不是对所有患者都有效,而且可能会带来一些副作用,例如疲劳、皮肤反应、口腔溃疡等。因此,在使用瑞戈非尼联合放疗治疗 CRC 时,需要综合考虑患者的病情、治疗目的、副作用等因素,制定个体化的治疗方案。同时,针对瑞戈非尼联合放疗及免疫对比单药瑞戈非尼在治疗转移性 CRC 患者中疗效策略的试验也在进行中[28]。

3　结　语

瑞戈非尼的临床应用为晚期 CRC 患者提供了更广泛的治疗选择,从肿瘤全程管理的角度来讲,或可考虑将其提前到二线治疗中使用,以期为患者带来更多生存获益。另外,CRC 的防治是迫切需要解决的问题,而瑞戈非尼已经被证实能够使血管正常化,同时可以改善肿瘤微环境,因此能够与免疫检查点抑制剂发挥更强的协同抗肿瘤效应。正因如此,瑞戈非尼与免疫治疗的联合方案被临床寄予厚望。除此以外,其他靶向、免疫治疗联合的探索仍在继续,为能发掘改善 MSS 型转移性 CRC 免疫微环境的联合治疗方案,未来还需从基础研究和转化研究深入探索不同药物的联合作用机制,开展大规模临床研究,以提高这一部分人群的生存获益。

然而,由于临床试验的局限性,瑞戈非尼的长期疗效和安全性仍需进一步观察和研究。此外,对于不同患者群体的适用性和剂量调整等问题也需要更多的实践和研究来解答。总的来说,瑞戈非尼是一种具有前景的药物,但需要在更广泛的临床实践中进一步评估和优化。

利益冲突　无

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收稿日期:2023-11-30 **修回日期**:2024-03-04 **编辑**:石嘉莹