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The analysis of targeted therapies for colorectal cancer with KRAS G12C mutation

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Abstract. *Kirsten rat sarcoma (KRAS) gene* G12C is a substitution mutation that causes colorectal cancer (CRC). This mutation keeps the KRAS protein at an active state, leading to the promotion of pro-tumorigenic downstream signals. Sotorasib and adagrasib are targeted therapies that covalently bind to the mutant C residue and cause irreversible inhibition of the mutant protein. While their monotherapies have already shown anti-tumour effects on CRC, clinical trials have demonstrated that sotorasib-panitumumab and adagrasib-cetuximab combined therapies can synergistically treat CRC. Nevertheless, life-threatening treatment-related adverse events (TRAEs) were observed in a few patients at a predicted level. Intrinsic and acquired drug resistance are the biggest obstacles; molecular triggers and secondary mutations make sotorasib and adagrasib no longer bind the targets. This paper evaluates monotherapies and combined therapies for KRAS G12C mutant CRC using a literature review and theoretical analysis. Selecting inhibitors such as SHP2 and SOS1 inhibitors, respectively, for co-inhibition was suggested as the solution to the problem.

Keywords: Colorectal cancer, *KRAS* G12C mutation, Sotorasib, Adagrasib.

1. Introduction

CRC is defined as the fourth most lethal cancer globally, constituting 9.2% of worldwide deaths. According to the latest WHO international cancer research, both the incidence and mortality rates of females are about 25% lower compared to males [1-2]. The epidemiology of CRC differs greatly based on region, age, gender, and race [3]. Besides being male or aging, common risk factors for CRC include a positive family history as well as environmental causes [1].

The KRAS gene is a member of the RAS family, and its mutations are genetic drivers of various cancer types involving CRC [4]. It occurs in roughly 40% of CRCs, with KRAS-G12 mutations being the primary cause [5-7]. The KRAS G12C mutation is a substitution mutation where glycine (G) is replaced by cysteine (C) at position 12, and this accounts for 3% of the CRCs [5,6,8,9]. This specific mutation generally leads to a challenging situation in the CRC, along with serious symptoms and low survival rates [10–12].

Epidermal growth factor receptor (EGFR) inhibitors are effective targeted therapies for RAS wild-type (WT) CRCs but showed no effect on KRAS G12C mutant CRC [8,9]. Studying the oncogenic KRAS signaling pathways, which are responsible for tumour cell proliferation and survival, could provide valuable insights into CRC therapeutics [13]. Sotorasib is a newly developed molecule designed to irreversibly inhibit the KRAS G12C mutant protein in specific [14]. It has already been shown to

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encourage anticancer activity in CRC patients as well as solid tumours [15]. Adagrasib, another KRAS G12C mutation-targeted drug, has demonstrated its antitumour effect as an oral monotherapy [16,17].

Recently, researchers have emerged and investigated combination therapies with either sotorasib or adagrasib. Adagrasib combined with an EGFR inhibitor, cetuximab, has been tested under KRAS G12C mutant CRC clinical trials [16], while sotorasib plus panitumumab, another EGFR monoclonal antibody, showed longer progression-free survival than standard treatment [18]. This paper, using the methods of literature review and theoretical analysis, evaluates the effectiveness, side effects, and resistance of the drugs as well as their combination therapies on KRAS G12C mutant CRC.

2. Pathology and targeted therapies

2.1. KRAS G12C Mutation

In normal cells, the KRAS protein acts as a signaling GTPase that alters between inactive GDP-bound and active GTP-bound states [19]. The loading of GTP on KRAS is catalysed by the guanine nucleotide exchange factors (GEF), while the GTPase-activating proteins (GAP) promote GTP hydrolysis [20,21]. KRAS activation usually initiates various signaling pathways, notably the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway [22]. In the KRAS G12C mutation, the C is positioned adjacent to the P2 pocket, which blocks the association between KRAS and GAP, thus the GTP hydrolysis [22,23]. This results in the KRAS becoming continuously active, therefore elevating the tumour-promoting signals [23]. Besides the EGFR inhibitors targeting downstream signaling pathways, such as the MAPK pathway indirectly, an extensive investigation has focused on inhibitors that are covalently bound to the mutated C residue in the P2 pocket [23,24].

2.2. Sotorasib

Sotorasib (AMG510 or Lumakras) is a targeted therapy developed by Amgen that covalently binds to the mutant C residue in the KRAS G12C protein and causes irreversible inhibition [14,24,25]. This maintains the protein in its inactive GDP-bound conformation, thus interfering with pro-tumorigenic downstream signalling [14,26]. Clinical studies have demonstrated mutant-selective tumour inhibition by sotorasib both in vitro and in vivo [14,24,27]. For instance, it only inhibits the growth of KRAS G12C-mutant-patient-derived xenografts instead of the KRAS G12V mutant one [14]. A phase 1 CodeBreaK100 trial (NCT03600883) revealed sotorasib as a clinical monotherapy on KRAS G12C mutated solid tumours. The KRAS G12C mutant CRC cohort showed a 7.1% objective response rate and a median progression-free survival of 4.0 months [15]. The phase 2 CodeBreaK100 trial, which provides 960mg sotorasib to the KRAS G12C mutant CRC patients, indicated a higher 82% disease control rate with a 9.7% objective response rate, along with a noticeable 66% tumour shrinkage [26]. Despite the reported higher response rate, only 10% of the 62 patients showed a partial response, failing to meet the lower limit of the 95% confidence interval (CI) and the primary endpoint.

Apart from sotorasib monotherapy, combination therapy with panitumumab, an EGFR inhibitor, was suggested to be an effective therapeutic [18,28-29]. One phase 1b CodeBreaK101 trial (NCT04185883) on KRAS G12C mutant CRC patients has utilised this strategy, and the combination was tolerable. The dose-expansion cohort had a 30% confirmed partial response, as well as a median 5.7-month progression-free survival [28]. These results align with a phase 3 CodeBreaK300 trial (NCT05198934), where either 960 mg or 240 mg sotorasib-panitumumab have been given to the KRAS G12C mutant CRC patients once a day, and 26.4% and 5.7% objective response rates were observed, respectively [18]. After extensive treatment with sotorasib and panitumumab, a male patient with KRAS G12C mutant metastatic CRC achieved a 12-month progression-free survival, following local interventions for oligoprogressive lesions [29]. Overall, these emphasize the significance of sotorasib-panitumumab combined therapies on KRAS G12C mutant CRC and highlight the potential for local interventions after the drug treatments.

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2.3. Adagrasib

Another well-known KRAS G12C inhibitor that shares similar mechanisms to sotorasib, which generates an irreversible covalent bond with the mutant C residue, is adagrasib (MRTX849), developed by Mirati Therapeutics. It also blocks the mutant KRAS protein in its inactive state and is consumed orally [30]. A study excluding CRC patients' samples has demonstrated that adagrasib is able to produce a 35% objective response in solid KRAS G12C mutant tumours [31]. In contrast to sotorasib, clinical trials of adagrasib were focused more on non-small cell lung cancers (NSCLC) than CRC [32-33].

A phase 1-2, nonrandomized clinical trial, KRYSTAL-1 (NCT03785249), comparing the effectiveness of 600 mg adagrasib monotherapy and its combined therapy with cetuximab on KRAS G12C mutant CRC patients was carried out. The results were expected since the combination therapy brought a 46% response rate and a median 6.9-month progression-free survival, which are higher and longer than the 19% and median 5.6-months generated by the monotherapy [16]. Also, the randomized phase 3 clinical trial KRYSTAL-10 (NCT04793958) is still in process. It compares how well adagrasib-cetuximab combined therapy works versus chemotherapy in treating KRAS G12C mutant CRC patients [34].

3. Discussion

3.1. TRAEs

TRAEs reflect the negative side effects or complications that occur from the medical treatment [35]. For sotorasib monotherapy, a grade 3 or 4 TRAEs has occurred in 11.6% of the patients [15]. In comparison, the sotorasib-panitumumab combined therapy demonstrated a grade 3 or higher TRAEs in around 30% to 35% of the KRAS G12C mutant CRC patients with lower to higher doses of sotorasib [26]. In addition, skin-related toxic effects and hypomagnesemia were the most frequently observed side effects of the combined therapy [26]. For adagrasib monotherapy and its combined therapy with cetuximab, the paper reported no death-related grade 5 TRAEs, but 34% and 16% grade 3 or 4 TRAES, respectively [16].

Grade 3 or 4 TRAES refers to severe or life-threatening consequences. Nevertheless, these percentages recorded during the clinical trials were as predicted with no treatment discontinuation [15,16,26]. Remarkably, the combination of sotorasib and panitumumab might exacerbate their effects on KRAS and EGFR pathways that are significant to skin repair and maintenance, thus causing dermatological side effects. As adagrasib-cetuximab exhibited fewer side effects, patients' variations, such as magnesium levels, should be considered. While adagrasib is a CYP3A4 substrate, patients should avoid its simultaneous use with CYP3A inducers; otherwise, its effectiveness will be lowered. Adagrasib taken with CYP3A inhibitors before the drug reaches its steady state, on the other hand, could raise the concentration of adagrasib, which would increase the risk of side effects [36].

3.2. Resistance

The greatest challenge to KRAS G12C inhibitor treatment is drug resistance [37, 38]. Acquired resistance to sotorasib and adagrasib has been reported in KRAS G12C mutant CRC or NSCLC patients, where RAS-MAPK reactivation was identified through several mechanisms [39]. Transacting mutations G13D in KRAS and R68S secondary mutations within the P2 have been identified, which aligns with the study that utilized Ba/F3 models searching for KRAS alternations that lead to inhibitor resistance (38). Another secondary KRAS Y96D mutation has also been identified with resistance to adagrasib, which matches the study [38,40]. R68 forms a cation-π bond with the azaquinazoline base of sotorasib, while Y96 is positioned at the entry point of the hydrophobic pocket where sotorasib and adagrasib bind. The mutations thus distort the binding sites, making the drug attachment unavailable. Furthermore, EGFR, phosphatase SHP2 signaling, and aurora kinase A (AURKA) were the molecular triggers that are responsible for maintaining the KRAS in a drug-resistant state [41-42].

To overcome either intrinsic or adaptive drug resistance, exploring both upstream and downstream of the RAS pathways is necessary. Co-inhibition, which inhibits SHP2 with KRAS G12C simultaneously, was considered more efficient than downstream co-inhibition [37]. The SHP2 inhibitor,

RMC-4630, has been tested with an MEK inhibitor called combimetinib, and the anti-tumour effect was shown in 37.5% of KRAS-mutant CRC patients [43]. In addition, researchers found that adagrasib and cell cycle checkpoint co-inhibition using the CDK4/6 inhibitor palbociclib enhanced the effect [44]. Meanwhile, researchers believed that sotorasib, when combined with immune checkpoint inhibitors like PD-1 inhibition, had a synergistic impact in mice [14]. For the KRAS secondary mutations, selecting SOS1 inhibitors to prevent RAS reactivation would be a choice [38].

4. Conclusion

In conclusion, sotorasib and adagrasib, which form covalent bonds with the C residue on the P2 pocket of the KRAS G12C mutant protein, exhibited a great anti-tumour effect on CRC patients. Phase 1b and 3 clinical trials on 960 mg sotorasib and panitumumab combined therapies have demonstrated their synergistic effect on CRC patients with a considerable objective response rate and progression-free survival. Despite the ongoing phase 3 clinical trial, the adarasib-cetuximab therapy has already demonstrated its positive impact on NSCLC.

Life-threatening grade 3 or 4 TRAEs were observed in a small number of patients. Although the number was as expected, side effects such as hypomagnesemia and skin-toxic outcomes should be noted. Drug resistance is the most concerning topic, accompanied by intrinsic and acquired mechanisms. Molecular triggers such as SHP2 signaling and secondary mutations such as KRAS Y96D share the same responsibilities. Co-inhibition, not only upstream or downstream, but also at cell-cycle and immune checkpoints, was able to reverse the RAS reactivation caused by intrinsic resistance to sotorasib and adagrasib. Meanwhile, SOS1 inhibitors were used to prevent the acquired drug resistance. Nevertheless, clinical trials testing co-inhibition together with sotorasib, adagrasib, or their combined therapies have not been carried out yet, and this should be one of the most focused aspects of overcoming drug resistance. Besides, future studies could explore biomarkers predicting the response of patients to the therapies as well as how their tumour microenvironments influence resistance. These can contribute to the development of personalized medicine for specific KRAS G12C mutant CRC patients.

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