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BRAF-directed Therapy in Metastatic Colorectal Cancer

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Abstract

Activating BRAF mutations occur in approximately 5–10% of metastatic colorectal cancer (mCRC) patients, mostly V600E mutation, and it is associated with distinct clinical and pathological features. To date, there are no approved treatments to target this mutation. BRAF inhibitor monotherapy has limited efficacy, in contrast to metastatic melanoma. Combination strategies that block not only BRAF mutated kinase but other alternative pathways are ongoing and have demonstrated improved activity. This review aims to provide data about new strategies to target to BRAF gene mutation in mCRC.

Keywords

colorectal cancer; BRAF inhibitor; mutation; biomarker; targeted therapy

Introduction

It has been now established that colorectal cancer (CRC) arises as a consequence of multiple genetic and epigenetic events that drive the transformation of normal colonic epithelium to cancer. Multiple pathways are proposed in this tumorigenesis; including Epidermal growth factor receptor (EGFR) pathway, Wnt signaling pathway, Transforming growth factor (TGF)-Beta signaling pathway, Notch signaling pathway, and Mitogen-activated protein kinase (MAPK) pathway. Precision therapy in colorectal cancer requires knowledge about the driven genes and the therapy to those genes.

BRAF encodes a serine/threonine protein kinase belonging to the RAS-RAF-MEK-ERK kinase pathway that has been implicated in pathophysiology proliferation, invasion, and metastasis in CRC.^{1, 2} The most common activating mutation is found in exon 15 at nucleotide position 1799, whereby a thymine (T) to adenine (A) transversion within codon 600 leads to substitution of valine by glutamate at the amino acid level. This leads to the

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oncogenic BRAF V600E mutation.³ BRAF V600E mutation leads to constitutive BRAF kinase activity, phosphorylation of MEK and ERK kinase and sustained MAPK pathway signaling. Other activating mutations in BRAF in CRC are very rare. The prevalence of this mutation is about 5–10% in mCRC.^{4–8} BRAF mutation tumors have been associated with female gender, advanced age, proximal colon tumor location, T4 tumors, poor differentiation, defective mismatch repair (dMMR) tumors and serrated adenoma pathway.^{9–11} They have poor prognosis and typically do not respond well to standard therapy with approximately 12 months of median survival.¹² Therefore, novel therapies for BRAF mutant CRC patients are needed.

Development of BRAF inhibitor in cancer treatment

The prototype to treat BRAF V600E mutant cancer was metastatic melanoma, a tumor subtype with higher rates (50%) of BRAF V600E mutations. Sorafenib, a multikinase inhibitor, was the first drug studied with the ability to inhibit several targets including BRAF V600E mutation. Although, this drug has activity against BRAF mutant metastatic melanoma in preclinical studies, it failed to demonstrate clinical efficacy in both single agent and combination with chemotherapy in phase II/III clinical studies.^{13–14} The data from phase I study with sorafenib at maximum tolerated dose showed no difference in the levels of phosphorylated MEK and ERK in pre- and post-treatment biopsies.¹⁵

Vemurafenib and dabrafenib, more potent and selective BRAF V600E inhibitors, have been approved by US FDA in 2011 and 2013; respectively for treating BRAF mutated metastatic melanoma based on increases in both progression free survival (PFS) and overall survival (OS) when compared to standard of care.^{16, 17}

The combination of dabrafenib and trametinib, targeting mitogen-activated extracellular signal-related kinase (MEK) which is downstream of BRAF in the MAPK pathway, was also approved by US FDA in 2014 based on increased PFS and OS over single dabrafenib or vemurafenib monotherapy.^{18, 19}

BRAF inhibitor monotherapy in mCRC

Although vemurafenib, dabrafenib, and trametinib have been approved for treating BRAF mutated metastatic melanoma, disappointingly, these drugs had only scant activity when used as a monotherapy in mCRC.

Vemurafenib has more potent and increases affinity selective BRAF mutated than sorafenib. Preclinical studies in BRAF mutant CRC cell lines, showed the ability of vemurafenib to inhibit MAPK signaling pathway²⁰. Kopetz, et al. reported a phase II study of vemurafenib in 21 mCRC patients with a response rate of only 5% (one partial response and seven stable disease). Median PFS and OS were 2.1 months (range 0.4 to 11.6) and 7.7 months (range 1.4 to 13.1), respectively.²¹ A similar result was shown with dabrafenib. Among 9 patients, one had a confirmed partial response (PR) and seven had stable disease (SD).²² Trametinib also showed no objective response in 28 mCRC patients²³, although this was not limited to BRAF mutant tumors.

Combination treatment

There are some data suggested that a combined treatment with BRAF and MEK inhibitor can lead to decreases MAPK signaling in BRAF mutant cell line.^{24, 25} Based on this knowledge, Corcoran, et al. evaluated the combination of BRAF and MEK inhibitor with dabrafenib and trametinib in 43 patients. Four (9%) achieved PR, one (2%) had complete response (CR) with duration of response more than 36 months and 24 patients (56%) achieved SD. Median PFS was 3.5 months (95% CI, 3.4 to 4). Analysis of tumor biopsy confirmed that combination regimen decreased downstream activation of MAPK pathway but not to the degree seen with single agent BRAF inhibition in melanoma.²⁶

The mechanism for resistance to the monotherapy has been proposed to be through feedback activation of MAPK signaling pathway. Two groups independently reported a possible mechanism through EGFR activation. The first group reported that single agent BRAF or MEK inhibitor cannot sustain the inhibition of the MAPK pathway in CRC cell lines. Negative feedback pathways can reactivate MAPK signaling through an increase in EGFR phosphorylation resulting in insensitivity to the drug.²⁷ Another group similarly demonstrated that vemurafenib increases activated EGFR activity, which reactivates the MAPK pathway.²⁸

In phase II study of vemurafenib in multiple non-melanoma cancer with BRAF V600E mutations (VE-BASKET trial), there were 37 patients with mCRC. 27 out of 37 patients were treated with vemurafenib plus cetuximab and 10 out of 37 patients were treated with single vemurafenib. The overall response rate in combination treatment was 4% (69% with SD) with median PFS and OS of 3.7 months (95% CI, 1.8 to 5.1) and 7.1 months (95% CI, 4.4 to not reach), respectively.²⁹ Yaeger, et al. also reported the pilot study of vemurafenib and panitumumab in 12 BRAF mutant CRC patients which showed the response rate of 13% with 53% of SD.³⁰

Overall, the data with combination of BRAF inhibitor and MEK or EGFR inhibitor suggest an improvement in efficacy over BRAF inhibitor monotherapy. However, some patients still do not response to these treatments which may reflect that dual combination therapy may not enough for suppress the signaling. Adding the third agent which uses EGFR+BRAF inhibitor backbone can improve the response in this group. Atreya, et al. reported the data from 35 patients with BRAF mutant CRC that use triple combination of dabrafenib, panitumumab and trametinib showed response rate of 26% with additional 57% of stable disease, which was higher than the combination of two drugs.³¹

Other pathways

Other than the MAPK pathway, the activation of phosphatidylinositol 3-kinase (PI3K)/AKT pathway has also been implicated resistance to BRAF inhibitor both melanoma³² and CRC cell line.³³ In mice xenografts model, treatment with vemurafenib and PI3K inhibitor showed higher rate of tumor growth inhibition when compare with vemurafenib alone. However, preliminary data from phase II study in combination of PI3K inhibitor with BRAF

and EGFR inhibitor did not demonstrate a convincingly higher response rate than the BRAF and EGFR combination alone (ORR 32 vs 23%, respectively) and no improvement in PFS.³⁴

Loss of function of APC gene leads to activation of canonical Wnt signaling pathway which is one of the major causes of CRC tumorigenesis. In a minority of patients, Wnt signaling is activated by alternative mutations besides APC. One example of this is RNF43 which encodes an E3 ubiquitin ligase that negative control Wnt signaling.³⁵ Analysis of The Cancer genome Atlas (TCGA) CRC data set reveals a co-occurrence of BRAFV600E mutation and RNF43 mutation. Data from translation and preclinical studies suggest that Wnt pathway signals together with EGFR-MAPK pathway may promote tumor growth in BRAF V600E CRC.³⁶ A clinical trial with a small molecule porcupine inhibitor, a Wnt inhibitor, combined with BRAF and EGFR inhibition is ongoing.

Other than proliferation pathway, suppression of apoptotic signaling contributes substantially to tumor progression. Overexpression of the pro-survival B-cell lymphoma 2 (Bcl-2) family members enhanced the survival of the cells by inhibiting apoptosis.³⁷ A previous study demonstrated that loss of apoptotic signaling significantly hinder the response to targeted therapies in BRAF mutant CRC.³⁸ There is an ongoing study which uses a Bcl-2 family inhibitor in combination with BRAF and EGFR inhibition in this subgroup.

Future direction

It is likely that optimal blockage of the MAPK pathway with dual or triple drug can lead to significant clinical benefit. There are initial results from the studies suggesting that the combination with anti-EGFR antibody and BRAF inhibitor with MEK inhibitor, PI3K inhibitor, BCL2 inhibitor or irinotecan might be more effective than two drug.^{31, 34, 39, 40} In addition, ERK inhibitor showed efficacy in reversing resistance in vitro⁴¹ and are also in early phase of clinical trial.

Here are the combination treatment strategies in BRAF mutant CRC (Figure 1), actionable drugs in proliferative pathway (Figure 2) and currently ongoing studies that combine multiple potential drugs for BRAF mutant mCRC (Table 1).

Summary

BRAF mutated CRC is an aggressive subpopulation of mCRC. Despite recent advances in the knowledge at the molecular level of CRC, the prognosis in this group remains poor. Unlike BRAF mutated melanoma, BRAF inhibitors monotherapy have been reported ineffective in mCRC. MAPK reactivation is a key mechanism of acquired resistance. The strategies that sustain inhibition of MAPK signaling pathway could control tumor proliferation and lead to an increase in survival. Therefore, treatments with BRAF-directed combination therapies may meaningfully change the outcome in BRAF mutated CRC patients.

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Figure 1.

The combination treatment strategies in BRAF mutant CRC

CRC=colorectal cancer; EGFR=epidermal growth factor receptor; BRAF= V-raf murine sarcoma viral oncogene homolog B; MEK=mitogen-activated extracellular signaling kinase; PIK3CA= phosphatidylinositol 3-kinase, catalytic subunit alpha; Bcl-2= B-cell lymphoma 2; i, inh.= inhibitor

Figure 2.
Actionable drugs in proliferation pathway that have been evaluated in BRAFmut CRC

Table 1

Ongoing clinical trials for BRAF mutant CRC

Categories	Phase	Study code	Study drug
1. EGFRi+BRAF+CMT	I	NCT01787500	Irinotecan + Cetuximab with or without Vemurafenib
2. EGFRi+BRAF+CMT	II/III	NCT02164916 (SWOG 1406)	Irinotecan + Cetuximab with or without Vemurafenib
3. EGFRi+BRAF+MEKi	I/II	NCT01750918	Panitumumab + Dabrafenib +Trametinib
4. EGFRi+BRAF+PIK3CAi	II	NCT01719380	Cetuximab + LGX818 (Encorafenib) with or without BYL719 (Alpelisib)
5. EGFRi+ BRAFi+ porcupine inh.	I/II	NCT02278133	Cetuximab + LGX818 (Encorafenib)+ WNT974
6. BRAFi+MEKi+Bcl2i	I/II	NCT01989585	Dabrefenib+Trametinib+Navitoclax
7. EGFRi+BRAF	I/II	NCT01086267	Cetuximab+BMS-908662 (XL281)
	II	NCT01791309	Panitumumab+ Vemurafenib

CRC=colorectal cancer; EGFR=epidermal growth factor receptor; BRAF= V-raf murine sarcoma viral oncogene honolog B; MEK=mitogen-activated extracellular signaling kinase; PIK3CA= phosphatidylinositol 3-kinase, catalytic subunit alpha; Bcl-2= B-cell lymphoma 2; CMT=chemotherapy; i, inh.= inhibitor