Published in final edited form as:
J Natl Compr Canc Netw. 2012 November 1; 10(11): 1456–1458.

BRAF Mutations in Colorectal Cancer: Clinical Relevance and Role in Targeted Therapy

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Introduction

It has long been appreciated that the clinical entity we call colorectal cancer is a phenotype which is made up of numerous different genotypes, accounting for the wide variation in clinical course and responses to therapies experienced by different individuals. Observations reported by Khambata-Ford et al and subsequently confirmed by Amato et al have made the practicing community aware that activating mutations in exon 2 of the gene encoding for KRAS, a key signal transduction protein, result in primary resistance to anti-epidermal growth factor receptor (EGFR) agents by leading to EGFR-independent activation of mitogen-activated protein kinase (MAPK) signaling.[1,2]

BRAF is a signal transduction protein which is downstream of KRAS in the MAP-Kinase pathway. Approximately 5–10 percent of colorectal cancers harbor mutations in BRAF, the most common of these being the V600E mutation. The occurrence of these mutations in colorectal cancers raises two important questions: what are the clinical characteristics of a colorectal cancer with a V600E BRAF mutation, and can that mutation be targeted for therapeutic advantage?

BRAF as a prognostic and predictive marker

From a prognostic perspective, it is clear that BRAF mutations confer a particularly poor prognosis, regardless of the therapeutic intervention used. In a combined analysis of the CRYSTAL and OPUS trials, two trials exploring the addition of cetuximab to front line chemotherapy for metastatic colorectal cancer, a substantially diminished overall survival for the BRAF mutated versus BRAF wild type patients was seen.[3]

The question of BRAF as a predictive marker of resistance to anti-EGFR monocolonal antibodies has been addressed, however the results are complicated. In the chemotherapy-refractory setting, responses to cetuximab or panitumumab in BRAF-mutated tumors are extremely rare. Di Nicoloantonio et al reported that in the chemotherapy-refractory setting, BRAF mutation confers resistance to cetuximab or panitumumab, with no responses in the 11 patients reported.[4] An additional study reported zero of five patients with BRAF-mutated tumors achieving a response, and found that progression-free survival was significantly shorter than that seen in BRAF wild type tumors. [5] De Roock et al reported a response rate of 8.3% (2/24) in patients whose tumors had BRAF mutations versus 38.0% in BRAF wild type tumors (124/326; p=0·0012).[6] Adding these three studies together, two of a total of 40

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BRAF-mutated tumors achieved a response, suggesting that the salvage activity of anti-EGFR agents in V600E BRAF-mutated tumors is similar to that seen in KRAS-mutated tumors.

More recent data from the combined analysis of the CRYSTAL and OPUS trials have raised questions about the potential for activity of anti-EGFR agents in conjunction with active chemotherapy in the front line setting in BRAF-mutated tumors.[3] It should be noted that these data are derived from an un-preplanned analysis of an un-preplanned combination of these two trials, each of which utilized a different chemotherapy backbone (FOLFIRI vs. FOLFOX) and each of which has a different pre-specified primary endpoint (overall survival versus progression-free survival), so the statistical validity of the observations is less than optimal. Nevertheless, while BRAF was, as mentioned above, a consistently poor prognostic marker, those patients who received cetuximab appeared to fare better in terms of overall survival (14.1 vs. 9.9 months) and progression-free survival (7.1 vs. 3.7 months) than those who received chemotherapy alone. As would be expected from the small numbers of patients involved, these differences do not reach statistical significance. This observation will require confirmation in prospective randomized trials; however the possibility of some clinically meaningful degree of activity of the first line addition of cetuximab or panitumumab to initial chemotherapy in patients with BRAF-mutated colorectal cancer cannot be excluded.

BRAF as a therapeutic target

The selective BRAF inhibitor vemurafenib (formerly known as PLX-4032) has achieved high response rates and increased overall survival in patients with BRAF V600E mutated melanoma[7]. The experience in colorectal tumors with BRAF V600E mutation has revealed only minimal activity of this agent in colorectal cancer, however. Kopetz et al treated 21 patients with V600E BRAF mutations with single agent vemurafenib; only one patient achieved an objective response[8].

Preclinical studies are investigating the reasons for this lack of activity in metastatic colorectal cancer. Pharmacodynamic studies in tumor samples from patients with melanoma treated in the phase I trial of vemurafenib indicate that near complete inhibition of pathway signaling is necessary to effectively inhibit tumor growth.[9] Two recent reports suggest that vemurafenib treatment fails to sufficiently inhibit BRAF in colorectal cancer because of reactivation of EGFR signaling[10],[11]. In a process of “adaptive resistance,”[12] when vemurafenib inhibits BRAF , it reactivates growth factor receptors previously suppressed by BRAF, which in turn can then re-activate BRAF and limit the efficacy of vemurafenib. Colorectal tumors have high relative EGFR expression and ligand production and therefore are primed for continued growth despite treatment with vemurafenib, experiencing this adaptive resistance much more rapidly than melanoma.

This adaptive resistance effect is likely magnified by the selective efficacy of current BRAF inhibitors such as vemurafenib. Vemurafenib inhibits mutated BRAF only, and mutated BRAF signals as a monomer. Paradoxically vemurafenib has been shown to activate MAPK signaling in tumors with wild-type BRAF, where RAF signals as a dimer[13]. As EGFR signals through RAS, feedback reactivation of EGFR with vemurafenib will lead to RAS activation and the formation of dimers of the RAF protein, against which vemurafenib is ineffective. Based on these data, we have proposed new studies which will test the clinical efficacy of combining EGFR and BRAF inhibitors in patients with BRAF-mutant colorectal cancer.

Conclusion

Our understanding of the prevalence and relevance of BRAF mutations in colorectal cancer continues to evolve. Available evidence strongly suggests that BRAF-mutant colorectal cancers carry a poor prognosis, and that these tumors are insensitive to EGFR inhibition in the chemotherapy-refractory setting to a similar degree as are tumors with exon 2 KRAS mutations. Intriguing, albeit suboptimal, data have raised the possibility of some degree of activity of EGFR agents in conjunction with active chemotherapy in frontline management of metastatic BRAF-mutated colorectal cancer. Vemurafenib, the selective inhibitor of mutated BRAF which has shown important single agent activity in V600E BRAF-mutated melanoma, is virtually inactive as a single agent in colorectal cancers harboring that same mutation. The reasons for this, and strategies to overcome that resistance, are the subject of ongoing investigations.

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