BRAF Mutated Metastatic Colorectal Carcinoma (mCRC): A case report

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ABSTRACT

Colorectal cancer (CRC) is the third and second most frequent cancer in men and women respectively. Although histologically similar, CRCs are diverse with respect to the underlying molecular mechanism which could be explored for planning treatment strategies. Chromosomal instability, microsatellite instability, and errors in the DNA repair mechanism are the most frequent molecular aberrations involved in various sub groups of CRCs.

BRAF(v-Raf murine sarcoma viral oncogene homolog B) mutation is seen in 5-15 % of CRC, with a higher mutation rate in right sided colon cancer. Patients with BRAF V 600E mutation tends to have a poor prognosis with a median survival rate of less than 12 months. In terms of treatment these patients do not benefit from therapeutics targeting the EGFR so it is important for clinicians to be aware. Treatment options beyond standard chemotherapy are crucial to achieve better outcomes and the role of anti-EGFR therapy alone remains controversial. Current trials assessing combinations of molecular targeted agents have shown some promise.

We report a case of a 32 year old female who presented with features of intestinal obstruction and pallor of skin and mucous membranes. Her blood test showed low Hb and a high serum CEA value and CT Abdomen revealed a large hepatic flexure growth with multiple liver metastasis. Colonoscopic biopsy showed moderately differentiated adenocarcinoma and molecular assay confirmed wild type K RAS and mutated BRAF. To the best of our knowledge there are no reported cases of BRAF mutated metastatic carcinoma colon from Nepal.

KEYWORDS

Colorectal cancer, BRAF mutation, chemotherapy, EGFR

INTRODUCTION

Colorectal cancer (CRC) remains one of the main causes of cancer mortality around the world. Although global mortality is decreasing, an increased mortality in young adults (<50 years old) has been reported.[1] The RAF kinase family consists of key components of the RAS–RAF–MEK–ERK signaling cascade (Figure 1) . Like RAS, the serine/threonine-protein kinase BRAF is a downstream signaling protein in the epidermal growth factor receptor (EGFR)-mediated pathway; in vitro experiences have highlighted that some genes are differently expressed in BRAF-mutant and wild-type CRC cell lines.[2,3] A characteristic gene expression signature associated with BRAF mutation has been identified.[4] However, attempts to directly inhibit the active BRAF protein failed in metastatic CRC (mCRC),[5] suggesting a more complex (or at least different) carcinogenic process in this disease. Nevertheless, BRAF mutation testing is now recommended for mCRC in the latest National Comprehensive Cancer Network guidelines.[6]

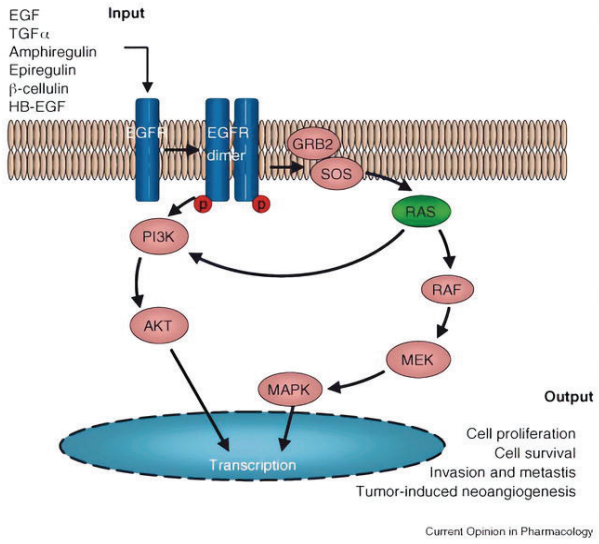

Figure 1: The MAPK pathway

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The MAPK pathway plays a major role in homeostasis of cellular proliferation, differentiation, survival, and apoptosis. Although the two genes work closely in the same pathway, the gene expression patterns of KRAS-mutant and BRAF-mutant mCRC are very different from each other.[7] Furthermore, the oncogenic contribution of mutated BRAF may vary between tumor types, as suggested by the very heterogeneous clinical benefit provided by BRAF inhibition treatment strategies in melanoma and mCRC.[5,8]

It has been reported that BRAF, and especially V600E mutations lead to constitutive BRAF kinase phosphorylation of MEK and ERK kinases and sustained MAPK pathway signaling. As soon as the RAF kinases are activated, MEK1 and MEK2 are phosphorylated and activated, and as a consequence ERK1 and RK2 are phosphorylated and activated.[9] This ERK activation produces phosphorylation of numerous substrates both in the nucleus and the cytosol, leading to an enhancement of cell proliferation and a longer survival.

EPIDEMIOLOGY

BRAF mutations are present in 5–15% of CRC, with a higher mutation rate in right-sided colon cancer.[10,11] In a report comprising 2530 patients with mCRC included in three randomized trials (COIN, FOCUS, and PICCOLO), the prevalence of BRAF mutations was 9.1%.[12] In a population-based study that could better reflect the true incidence, 12% of the patients had BRAF-V600E mutant tumors.[13] In another population-based report the percentage of BRAF-mutant tumors was even superior to 20%.[14] Dual mutations of RAF and RAS genes are rarely seen: Eight among the 2530 patients (0.3%) and 0.01% of cases in another series.[15] BRAF mutations (and KRAS) were approximately twice as likely to be found in the caecum than the sigmoid colon.[16]

IMPACT OF BRAF MUTATIONS ON PROGNOSIS IN METASTATIC DISEASE

The mechanism resulting to the poor prognosis of patients with BRAF-mutant mCRC is poorly understood. It was rapidly shown that with standard treatment including targeted therapies, the median OS of these patients was around 12 months, much lower than that obtained in BRAF-wild-type patients.[17,18] In a study evaluating 5FU/folinic acid/irinotecan (FOLFIRI) plus panitumumab in a pure second-line setting, patients with BRAF-mutant mCRC had a median PFS of 2.5 months and an OS of 4.7 months, compared with a PFS and an OS of 6.9 and 18.7 months, respectively, in patients with BRAF-wild-type tumors.[19]

FOLFOXIRI + BEVACIZUMAB AS FIRST-LINE TREATMENT OF BRAF-MUTANT TUMORS: A STANDARD OF CARE?

Despite a lack of evidence to back up the interest in the use of bevacizumab in combination with chemotherapy, the most interesting data obtained to date in BRAF-mutant mCRC resulted from a combination of triplet chemotherapy with bevacizumab. Following the results of the first large phase III trial of the GONO group, it has been known for 10 years that triplet chemotherapy with 5FU, folinic acid, irinotecan, and oxaliplatin (FOLFOXIRI) was able to improve efficacy to FOLFIRI in an all-comers patient population.[20] The same group evaluated the role of this combination plus bevacizumab. They reported a very good response rate (90%), median PFS (12.8 months), and OS (30.9 months) in a subgroup of 10 patients with BRAF-mutant tumors treated with FOLFOXIRI + bevacizumab (post hoc analysis).[21]

TREATMENT OF BRAF-MUTANT TUMORS AFTER FAILURE OF FIRST-LINE THERAPY

Beyond the first line, despite the failure of RAF inhibitor monotherapy, some second-line treatments, such as the combination of vemurafenib, irinotecan, and cetuximab, have shown activity. Thus, a sequential use of FOLFOX bevacizumab followed by irinotecan, 5 FU, vemurafenib, and cetuximab is the other valid option.

CASE PRESENTATION

A 32 year old , normotensive and non diabetic lady, with no significant past medical and surgical history, and no familial history of colon cancer syndrome sought medical attention after she experienced sudden onset pain abdomen in the right side of the abdomen associated with significant weight loss for 1 month. A contrast enhanced CT scan of the abdomen showed moderately heterogenous asymmetric thickening of the hepatic flexure of the colon with features of intestinal obstruction and associated multiple liver metastasis. Her hematological and biochemical parameters were all within normal limits. Serological analysis showed raised serum CEA of 168.07 ng/ml. On colonoscopy a large ulcerative mass in the hepatic flexure was visualized, a biopsy of which showed moderately differentiated adenocarcinoma (Fig 2).

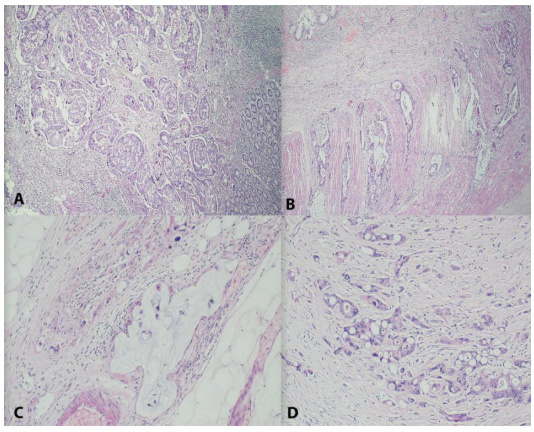

Figure 2 (HE stain, x10): A: Moderately differentiated adenocarcinoma in submucosa, normal colonic mucosa is

evident. B-C: The neoplastic glandular cell invades muscle layer up to serosa. Signet ring cells with foci of mucinous pool is seen. D: Neoplastic glandular cells show prominent desmoplasia.

She underwent right hemicolectomy with left lateral segmentectomy and metastectomy of liver. Histopathology also revealed moderately differentiated adenocarcinoma with infiltration upto pericolic fat with lymph node involvement(7/20), lymphovascular invasion with overall TNM staging of pT3N2M1(liver metastasis). Molecular testing showed KRAS- wild type disease, high MSI and BRAF V600E mutation.

After one month of post operative period she again developed right sided abdominal pain associated with nausea, vomiting , anorexia and significant weight loss. She was advised for a whole body PET scan in view of clinical progression of disease, finding of which was progressive liver and lymph node metastasis. (Figure 3).

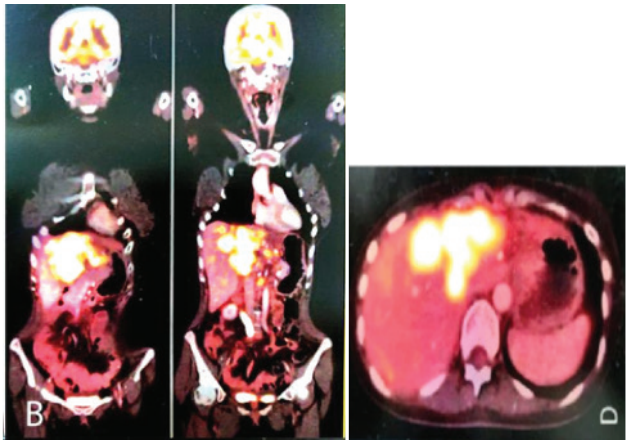

Figure 3 PET images showing multiple liver and nodal metastasis

She was subsequently initiated on FOLFIRI regimen (5FU, Leucovorin, Irinotecan) along with Vemurafenib, a BRAF inhibitor and Cetuximab, an anti-EGFR monoclonal antibody. She showed marked clinical improvement as evident by decrease pain abdomen, weight gain and a drop in CEA value to near normal(9 ng/ml) after two cycles of treatment. After radiological assessment she is planned for continuation of further chemotherapy, BRAF inhibition and anti-EGFR therapy.

DISCUSSION

BRAFV600E mutation in patients with CRC is a unique molecular subtype occurring in 10-15% of patients with mCRC and is associated with poor prognosis in the metastatic stage despite good early stage prognosis.[22,23] Hence, aggressive combination chemotherapy is required to improve the survival rate in patients with BRAFV600E mCRC.[24]

The standard therapy includes surgery followed by adjuvant chemotherapy in combination with targeted therapy, which improves overall survival (OS).[25] Sequential combination chemotherapy also plays an important role in CRC management, especially in mCRC.[26] Cytotoxic drugs such as 5-fluorouracil combined with oxaliplatin and irinotecan (FOLFOXIRI) are still the preferred chemotherapeutic regimen for mCRC.[27] They have a synergistic effect when combined with biological agents such as EGFR and BRAFV600E-specific inhibitors.[28]

Our patient presented with right sided colonic growth with multiple liver metastasis and was found to have BRAFV600E mutation and wild type K-RAS on surgical specimen. Her disease biology was very aggressive in nature as evident by her PET scan findings just after one month of surgery. She showed symptomatic improvement after treatment with BRAFV600E inhibitor- vemurafenib and anti- EGFR therapy- cetuximab along with the cytotoxic drugs irinotecan and 5-fluorouracil. Further radiological evaluation of this patient is planned after 6 courses of therapy.

The presence of only minor adverse events indicates that the drug combination is well tolerated in our case. Although we could not ascertain the long-term recurrence of mCRC and safety in our patient, the drug combination could be an option as first-line therapy for treating similar patients in our subset of patients in Nepal.

CONCLUSION

Patients with BRAF-V600E-mutant mCRC clearly have a poor prognosis and constitute a specific group, making up around 10% of all patients with mCRC. The exact prevalence of BRAF-V600E-mutated mCRC from Nepal is not known. Pooled analysis of similar cases need to done from different hospital based registries across the country. FOLFOXIRI + bevacizumab is a possible good treatment option. The role of the addition of anti-EGFR and BRAF inhibitor to FOLFIRI is also well documented as seen in our case. New drugs, new combinations, and new targets are urgently required in this subset of patients for a better outcome.

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