V600E and Non-V600E BRAF Mutations in Colorectal Cancer: Clinicopathologic Correlations in a Single Institution

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ABSTRACT

Genomic characterization of BRAF mutation in colorectal cancer (CRC) revolutionized it's management. Current knowledge regarding BRAF mutant CRC is based on the prevalent V600E mutation and mostly on Western population. However, CRC is known to be a complex and heterogenous disease. Thus, we aim to characterize the molecular, clinical and epidemiologic features of V600E as well as non-V600E BRAF mutated CRC in Turkish population. Demographic, histopathologic, molecular and clinical data of V600E and non-V600E BRAF mutant, metastatic and non-metastatic CRC cases were retrospectively collected from a tertiary Oncology hospital. Thirty cases of BRAF mutant colorectal carcinoma was identified. BRAF mutations were V600E (66.7%), V600A (10.0%), V600G (3.3%), V600K (3.3%), and L597V (16.7%). BRAF V600E cases had similar characteristics with Western population: frequent in females (45.0%), more proximal location (52.6%), aggressive histopathologic features (LVI 50.0%), and a worse prognosis (OS 13 vs 30 months, p= 0.068). Non-V600E BRAF mutant cases were diferred from V600E cases by being more frequent in males (50.0%), located more distally (60.0%), and carrying a better prognosis. This study demonstrates V600E mutation in CRC in Turkey is similar with Western population. In like manner, non-V600E BRAF mutation in CRC bears the potential to be a significant attribute for both prognostic and therapeutic implications as well.

Keywords: BRAF, V600E, Non-V600E, Colorectal carcinoma, Turkish

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related death and its mortality has decreased with the improved screening methods and treatment modalities through the past decades.[1] However, this longer survival has not been achieved for a fraction of cases, including BRAF mutated metastatic CRC, thus a better insight into these molecular subtypes is needed.

BRAF protein is a part of MAPK signaling, that takes part in cellular growth, differentiation, migration, and proliferation. Most frequent BRAF mutation in human cancer is the substitution of 600th codon valine by glutamic acid (V600E). This mutation, occurring in the glycine-rich P-loop, which includes the activation segment, increases the independent kinase activity of BRAF protein, thus results in downstream activation.[2-4] Other BRAF mutations with diverse activities were shown in various cancers, including malignant melanoma, non-small cell lung cancer, and Langerhans cell histiocytosis, with proposed clinical significance.[5-10]

Mutations in KRAS and BRAF proteins are the commonest ones among MAPK pathway in CRC, reported in 40% and 10% of cases respectively with a mutually exclusive manner. V600E ^{mt}BRAF in CRC (^{V600E}CRC) is diagnosed more frequently in female and elderly, more proximal, accompanied by lymphocytic infiltration, have mucinous and undifferentiated histology. More typically associated with serrated adenoma/methylation pathway, also has somatic microsatellite instability (MSI-H) and increased CpG island methylation (CIMP-H) phenotype. There is a great resemblance between ^{mt}BRAF CRC and Consensus Molecular Subtype 1 defined by Colorectal Cancer Consortium.[11] Non-V600E BRAF mutations in CRC (^{nonV600E}CRC) have also been defined. They were suggested to be different from ^{V600E}CRC as they are associated with male predominance, distal location, MSI-H phenotype, a longer OS with a lesser propensity of peritoneal metastasis. Thus non^{V600E}CRC was proposed to constitute a distinct subtype in CRC.[9,12]

BRAF mutation has impacts on prognosis and treatment in CRC. Microsatellite stable (MSS) ^{V600E}CRC was shown to carry a worse prognosis and has a shorter OS for both early and metastatic stage. They have poorer response to anti-EGFR and fluoro-pyrimidine based cytotoxic chemotherapy especially for stage II and III tumors, triple cytotoxic treatment have been advocated by some guidelines.[9,13] Response to anti-VEGF agents was found to be similar to BRAF wild-type tumors.[14] Newer therapeutic interventions such as combination molecular therapies targeting EGFR, RAF, MEK and PI3K molecules have been tested and reviewed extensively elsewhere.[15]

CRC is known to show geographic and racial disparities which is hypothesized to be induced by differences between genetic and environmental factors. Geographic heterogeneity of its incidence varying up to ten times between different continents is a convincing example.[16,17] Likewise, in ^{V600E}CRC, data from Middle-Eastern and Asian populations have mentionable divergences regarding incidence, epidemiology and molecular characteristics from pre-mentioned features of ^{V600E}CRC which were mostly derived from studies within Western populations.[18-20] Our current knowledge regarding ^{mt}BRAF in CRC in Turkish population is limited. Studies to date demonstrated 0% to 30% incidence, however scarcity on clinical and histopathologic aspects of the cases.[21,22]

Although mortality of CRC has been decreased with better screening and treatment, there is a mentionable fraction of patients who do not benefit from the current therapeutic options. This demonstrates that there are significant gaps in our ability in the management of CRC. Delineating the different subtypes of CRC will be a valuable mean to address those gaps. The study aims to further characterize the molecular, clinical and epidemiologic features of V600E and nonV600E BRAF mutated CRC in the Turkish population regarding the key research question of whether or not non^{V600E}CRC cases differ from ^{V600E}CRC, and Turkish ^{V600E}CRC differ from other data in literature.

MATERIALS AND METHODS

Study Design

This is a retrospective case-series. Colorectal cancer registry of a University-affiliated Oncology hospital was retrospectively evaluated between 01.01.2012 and 12.12.2015. Inclusion criteria required colorectal cancer patients to have carried a BRAF gene mutation and have evaluable records. Mutations were tested in different labs using PCR techniques. Patients' data including epidemiological, pathological, clinical, and survival were collected. Data gathered were analyzed with IBM SPSS® 25.0 using Pearson, Fisher, Mann-Whitney U and Log-Ranks tests.

RESULTS

BRAF Mutation Status

Of all colorectal cancer patients in the registry, 30 cases were found to be BRAF mutated. Most frequent mutation was V600E seen in 20 patients (66.7%). Second and third commonest ones were L597V and V600A, seen in 5 (16.7%) and 3 (10.0%) patients respectively. They were followed by two other mutations, V600K and V600G, both were seen in one (3.3%) patient. Consequently, 34.5% of the mutations in the population were non-V600E CRC(^{nonV600E}CRC). All cases were tested for RAS mutation and none were positive (Table 1).

Table 1. Subtypes of BRAF mutant colorectal cancer

BRAF Mutation	Number (%)
V600E	20 (66.7%)
L597V	5 (16.7%)
V600A	3 (10.0%)
V600G	1 (3.3%)
V600K	1 (3.3%)

Table 2. Histopathologic features of different BRAF mutant colorectal cancer subtypes

	V600E (n/%)	Non-V600E (n/%)
Mucinous differentiation	N/A	4 (40.0%)
Perineural invasion	3 (25.0%)	3 (42.9%)
Lymphovascular invasion	6 (50.00%)	3 (42.9%)
Microsatellite instability	2 (22.2%)	(0.0%)

Patient and Tumor Characteristics

Patients' age ranged from 19 to 79 years, with a median of 59.5, with slight male predominance (53.5%). The proportion of males were similar between ^{V600E}CRC group and ^{nonV600E}CRC groups (55.0% and 50.0%, p= 0.068).

Primary tumor location was distal colon in over half of all CRC cases (51.7%). Primary V600E-CRC tumors were located proximally (52.6%), in contrast ^{nonV600E}CRC tumors were mostly distal (60.0.6%) (p< 0.1).

Study population consisted of mostly metastatic cases (73.3%). For both ^{V600E}CRC and ^{nonV600E}CRC tumors, liver was the most common region for metastasis. Non-metastatic cases' T stages at presentation were T2 in 33.3%, and T3 in 66.7%. Lymph node metastasis were seen in 50.0% of patients, with 16.7% N1 and 33.3% N2. In non-metastatic cases, stage 3 was the most prevalent stage at presentation.

Pathological Characteristics

Mucinous differentiation was reported in 40% of $^{non-V600E}$CRC tumors. Perineural invasion washigher in ^{nonV600E}CRC (42.9%) than ^{V600E}CRC (25.0%)., Lymphovascular invasion was more frequent in $^{V600E-}$CRC patients (50.0%) than ^{nonV600E}CRC (42.9%). Epigenetic attributes could not be comprehensively evaluated due to the retrospective nature of our study. With the available data investigating MSH2, MSH6 and MLH1 expressions, ^{V600E}CRC and $^{non-V600E}$CRC patients showed 10% and 22% of MSI phenotype respectively (Table 2).

Tumor markers were as CEA above 5 ng/mL in 57.9% and CA 19-9 above 37 U/mL in 50.0% of cases. ^{V600E}CRC and ^{nonV600E}CRC did not differ in tumor marker expression (Table 3).

Clinical Characteristics

Regarding 12 non-metastatic (CRC^{nonmet}) patients at presentation, 6 patients' complete initial treatment regimens and radiological response data could be

Table 3. Characteristics of BRAF V600E and NonV600E CRC patients

		V600E (n/%)	Non V600E (n/%)	p
Gender	Male	11 (55.0%)	5 (50.0%)	0.796
	Female	9 (45.0%)	5 (50.0%)	
Age (Median)		62	58	
Metastasis Status	Non-metastatic	5 (25.0%)	3 (30.0%)	0.770
	Metastatic	15 (75.0%)	7 (70.0%)	
CEA Levels	< 5 ng/mL	6 (50.0%)	2 (28.6%)	0.361
	> 5 ng/mL	6 (50.0%)	5 (71.4%)	
Ca 19-9 Levels	< 37 U/mL	6 (46.2%)	4 (57.1%)	0.639
	> 37 U/mL	7 (53.8%)	3 (42.9%)	
Tumor Location	Distal	9 (47.4%)	6 (60.0%)	0.518
	Proximal	10 (52.6%)	4 (40.0%)	

Table 4. Treatments and responses of metastatic colorectal cancer patients

	Gender	Age	BRAF Mutation	Best Overall Response	Progression Free Survival	Overall Survival
FOLFOX	Female	52	L597V	Partial response	18	47
FOLFIRI	Female	74	V600A	Partial response	35	50
	Male	36	V600E	NA	NA	13
CAPECITABINE	Male	61	V600A	Stable disease	12	65
	Female	60	L597V	NA	NA	25
FUFA	Male	79	V600E	Progression	0	28
FOLFOX-BEVA	Female	54	V600E	Stable disease	19	22
FOLFIRI-BEVA	Male	58	L597V	Stable disease	13	33
	Female	41	V600E	Stable disease	6	7
	Male	62	V600E	Progression	6	12
	Female	65	V600E	Progression	3	5
	Male	53	V600G	Stable disease	13	24
	Female	52	V600K	Progression	12	21
	Male	61	V600E	Stable disease	6	37
FOLFIRI -CETUXIMAB	Female	46	V600E	Stable disease	NA	5
	Male	59	V600E	Stable disease	12	23

obtained, and is as follows: Three $^{nonV600E}CRC^{nonmet}$ cases treated with FOLFOX (folinic acid, fluorouracil, oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, irinotecan) regimens yielded a median progression-free survival (PFS) of 18 months and a median overall survival (OS) of 50 months. For two $^{V600E}CRC^{nonmet}$ $^{nonV600E}CRC^{nonmet}$ cases that were treated with FOLFIRI plus antiangiogenic agent, PFS were 13 months for the former and 31 months for the following. One $^{V600E}CRC^{nonmet}$ patient treated with fluoro-pyrimidines alone had a shorter PFS of 3 months.

For 22 patients with metastasis (CRC^{met}), 16 patients medical therapy was available for review and included regimens consisting of fluoro-pyrimidines alone or with cytotoxic or anti-angiogenic agents. One $^{V600E}CRC^{met}$ patient treated with only fluoro-pyrimidines had 6-month PFS and 15-month OS. Two $^{nonV600E}CRC^{met}$ patients had a OS of 25 and 65 months with single fluoro-pyrimidine. One $^{V600E}CRC^{met}$ patient was treated with FOLFIRI, the OS was 13 months, PFS could not be obtained. For the other two patients treated with FOLFIRI regimen, PFS were 8 and 14 months and OS were 29 and 32 months.

For thirteen patients who were administered FOLFIRI plus antiangiogenic treatment, V600ECRC-met patients' median PFS 6 months while non-$^{V600E}CRC^{met}$ has a 13 months with a statistically significant significance (p= 0.03). For the same treatment strategy, the median OS was 7 months for $^{V600E}CRC^{met}$ and 21 months for $^{nonV600E}CRC^{met}$ (p= 0.69). Best overall responses to specific regimens did not differ between $^{V600E}CRC^{met}$ and non-$^{V600E}CRC^{met}$ tumors for any of the various treatment strategies (p= 0.76) (Table 4).

For all BRAF mutant metastatic patients (CRC^{met}), median OS was 21.5 months, and median PFS was 10.0 months. Regarding different BRAF mutations, $^{V600E}CRC^{met}$ had a lower OS of 13 months compared to 30 months OS of $^{nonV600E}CRC^{met}$, although not reaching statistical significance (p= 0.068). Similarly, PFS of $^{V600E}CRC^{met}$ was also lower with 6.0 months compared to 11.5 months median PFS of $^{nonV600E}CRC^{met}$ (p= 0.078). For right and left side CRC^{met} tumors, right-sided tumors had a median OS of 21.4 months and had advantage over left-sided primary tumors with a median OS of 9.3 months (p= 0.032).

Pathologically lymphovascular invasion status, perineural invasion status, and MSI phenotype did not show any effect on OS or PFS. Similarly for clinical attributes; tumor's marker expression, location and initial region of metastasis did not differ regarding influence on PFS and OS with statistical significance.

Our one case has shown adenosquamous differentiation with BRAF V600E mutation. To the best of our knowledge, this is the first case in the literature. She was a 49-year-old female presenting colonic obstruction with peritoneal and liver metastases. The patient has died after five months of diagnosis because of ileus and post-renal acute renal failure.

DISCUSSION

BRAF mutation is now acknowledged as a consequential feature of colorectal cancer with impacts on prognosis and treatment. Nevertheless, its clinical utilization is still under debate probably owing to the fact that it embraces a heterogeneous group of tumors with also geographical diversity. In addition to that, as is known from other tumors, separate mutations on BRAF protein have different attributes.[7,8,10] The aim of our study is to delineate the specific characteristics of nonV600E BRAF mutations on colorectal cancer and also describe characteristic features of V600E BRAF mutated colorectal cancer in Turkish population.

In our study, male to female ratio was found to be 1.15 for overall ^{mt}BRAF tumors, for ^{V600E}BRAF it was 1.4. In Western populations BRAF mutation is known to be more frequent in females, although there are studies from Eastern populations showing male or no predominance.[23-26] Median age of our patients was 59.5 years, compatible with literature. For the location of primary tumor, ^{V600E}CRC tumors were more frequently located on proximal colon (60%), contrastingly ^{nonV600E}CRC tumors significantly had predilection for distal colon (%86.6) consistent with other studies regarding nonV600E tumors.[9] Lymphovascular and perineural invasion did not differ between ^{nonV600E}CRC and ^{V600E}CRC groups. Due to the retrospective nature of our study, our evaluation of the epigenetic attributes had to be limited. Our data indicate that MSI-H phenotype is also frequent in ^{nonV600E}CRC tumors.

Adenosquamous differentiation is a rare attribute comprising 0.5-2% of colorectal cancer.[27] It is more frequently seen in older age, male gender, and Caucasian population with a more advanced stage and undifferentiated histology, thus shorter OS. Correspondingly, our case is a 66 year-old male presenting with a rectal tumor and liver metastasic, and had a shorter OS of 5 months. To the best of our knowledge, this is the first case in literature reporting adenosquamous histology in a ^{V600E}BRAF mutant colorectal cancer.

In conclusion, for Turkish population, epidemiologic, pathologic and clinical characteristics of V600E mutation in colorectal cancer is consistent with literature with being seen more frequently in elderly and patients, proximal predominance, increased lymphovascular and perineural invasion, frequent MSI-H phenotype, and decreased overall survival.

There are only scarce data in literature regarding ^{nonV600E}CRC. First study on this matter reviewed 10 metastatic colorectal cancer cases with BRAF codons 594 and 596 mutations. The cases were found to be rectal and left colon predominant, with non-mucinous histology and lower tumor-grade, having microsatellite stability and a longer OS compared to V600E mutant tumors.[28] Another recently published study evaluated a retrospective cohort of 208 ^{nonV600E}CRC patients, encompassing wide range of mutations, yielded similar results: distal predominance, microsatellite stability and longer OS with addition of male predominance and lesser propensity of peritoneal metastasis.[9] Herein this study we have evaluated 11 cases of BRAF nonV600E mutant colorectal cancer, five of them being 597th codon mutated, remaining cases were mutated on 600th Codon. Considering all nonV600E BRAF mutations, our findings are partially compatible with previous studies as having less aggressive pathologic features, more propensity to be left sided and having a longer OS than V600E mutant tumors. Conversely ^{nonV600E}CRC cases did not differ from ^{V600E}CRC in terms of patient age and gender. 597th codon mutations are not distinct from other mutations in any way with statistically significance.

Uttermost pronounced limitation of our study is the low number of patients probably caused from the reported low prevalence of these mutations in colorectal cancer patients. Another further limitation is the retrospective nature of our study. There are also some missing data that was mentioned above resulted by unperformed further pathological evaluations deemed non-essential in clinical circumstances previously.

Much is known regarding V600E mutation in colorectal cancer (CRC): it is more frequently in female and elderly population, tumors tend to be proximal, histopathology is significant with lymphocytic infiltration and mucinous changes. Its genetic profile is high microsatellite instability (MSI-H) and increased CpG island methylation (CIMP-H) phenotype. Less is known for non-V600E mutation in CRC. Hereby in this detailed evaluation of non-V600E cases, we aimed to delineated this rare mutation in CRC. It was frequent in female and elderly, had predilection for distal colon, showed similar histopathologic attributes albeit with a better prognosis. Non-V600E BRAF mutation tends to carry a better prognostic significance and can be managed less aggressively.

Colorectal cancer is an important cause of cancer related mortality and morbidity. With our understanding of the footsteps of carcinogenesis, we have come a long way in its treatment. Nevertheless, ongoing discoveries of new molecular subtypes of colorectal cancer show that we have a long road ahead. Specifically, better knowledge of the mutations related to BRAF protein with higher patient numbers, longer follow-up periods and a more detailed genetic and pathologic analysis, has the potential to help us formulate new perspectives on treatment of colorectal cancer.

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