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Research Article

AGGF-1 Expression as a Predictive Biomarker for Anti-VEGF Therapy in Metastatic Colorectal Cancer

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Abstract

Objectives: Metastatic colorectal cancer (mCRC) remains a major therapeutic challenge, and predictive biomarkers for anti-angiogenic therapy are still lacking. Angiogenic factor with G-patch and FHA domain 1 (AGGF-1) is a pro-angiogenic protein that has been associated with unfavorable prognosis in several malignancies. However, its clinical significance in mCRC, particularly in patients receiving bevacizumab-based chemotherapy, has not been clearly defined.

Methods: This retrospective study encompassed 67 patients with mCRC who received first-line bevacizumab-based chemotherapy. Tumor specimens were evaluated for AGGF-1 expression by immunohistochemistry. AGGF-1 expression was assessed based on staining proportion and staining intensity.

Results: AGGF-1 expression was detected in 33 patients (49.3%) and was more frequent in de novo metastatic disease than in recurrent disease (p = 0.026). Patients exhibiting AGGF-1 expression demonstrated numerically reduced overall survival (OS) and progression-free survival (PFS); however, these disparities lacked statistical significance. In multivariate analysis, AGGF-1 staining intensity was independently associated with PFS (p=0.009). Location of the primary tumor predicted both OS and PFS, whereas metastasectomy correlated with enhanced OS.

Conclusion: AGGF-1 expression may be associated with unfavorable outcomes in bevacizumab-treated mCRC. Prospective studies are needed to clarify its prognostic value.

Keywords: AGGF-1, Bevacizumab, Colorectal Cancer

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Colorectal cancer is a molecularly heterogeneous disease characterized by driver mutations such as Kirsten rat sarcoma viral oncogene homolog (KRAS) and B-Raf proto-oncogene (BRAF), which influence treatment decisions and prognosis.[1] KRAS mutations are detected in a substantial proportion of cases and are known to confer resistance to epidermal growth factor receptor (EGFR)–targeted therapies. In addition, specific KRAS variants, such as G12C, have emerged as therapeutic targets.[2,3] However, tumor progression is not determined solely by oncogenic alterations. Interactions between tumor cells and the tumor microenvironment, particularly angiogenic pathways, also play an important role in metastatic spread and treatment response.

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Tumor angiogenesis is essential for colorectal cancer growth and dissemination. Inhibition of angiogenic pathways, especially through vascular endothelial growth factor (VEGF) blockade, has become an established component of treatment in metastatic disease.[4] Nevertheless, reliable predictive biomarkers for anti-VEGF therapy remain lacking.

Angiogenic factor with G-patch and FHA domain 1 (AGGF-1) is a pro-angiogenic protein initially described in Klippel–Trenaunay syndrome.[5,6] Subsequent studies have demonstrated AGGF-1 expression in several malignancies, including hepatocellular, gastric, and urothelial cancers, where it has been associated with tumor angiogenesis and unfavorable prognosis.[7–9] However, the predictive role of AGGF-1 expression in cancer therapy—particularly in the setting of anti-VEGF treatment—has not been clearly defined.

In patients with metastatic colorectal cancer (mCRC) receiving first-line therapy, bevacizumab—an anti-angiogenic agent targeting VEGF-A—has been widely incorporated into chemotherapy regimens. Although clinical trials have demonstrated improvements in progression-free survival (PFS) and, in some settings, overall survival (OS), treatment benefit remains variable among patients. Importantly, no validated predictive biomarker currently exists to identify individuals most likely to benefit from bevacizumab-based therapy.[10,11] Therefore, we aimed to investigate the association between AGGF-1 expression and treatment outcomes in patients with mCRC receiving first-line bevacizumab-containing chemotherapy.

Methods

We retrospectively identified patients with metastatic colorectal cancer who received first-line bevacizumab-based chemotherapy between March 2011 and August 2020 (n=111). Tumor specimens obtained at diagnosis from either the primary tumor or metastatic sites were retrieved from pathology archives. Forty-four cases were excluded due to insufficient tumor content in formalin-fixed, paraffin-embedded (FFPE) samples for AGGF-1 immunohistochemical (IHC) evaluation. The final study cohort consisted of 67 patients.

Participants in the study met the following criteria: histologically confirmed metastatic colorectal cancer (mCRC), age over 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and having undergone a minimum of four cycles of bevacizumab in combination with a 5-FU-based chemotherapy regimen as first-line treatment. Patients previously treated with chemotherapy or targeted therapy for metastatic disease, those with brain metastases, and those lacking treatment response evaluation were excluded from the study.

Tumor responses and progression were evaluated radiologically utilizing the Response Evaluation Criteria in Solid Tumors (RECIST), blood levels of CEA and CA 19-9, and patient-reported symptoms. PFS was established from the beginning of first-line systemic therapy to radiologic disease progression or death from any source. OS was established from the beginning of therapy to death from any cause; patients without an event were censored at the date of last contact.

Given the absence of prior studies evaluating AGGF-1 as a predictive biomarker in metastatic colorectal cancer, this investigation was designed as an exploratory analysis. IHC assessment was performed using predefined semi-quantitative criteria to ensure consistency in scoring. AGGF-1 expression was evaluated in FFPE tumor specimens retrieved from pathology archives, and all slides were reviewed by a single experienced pathologist to minimize interobserver variability. Cytoplasmic staining was assessed based on both the proportion of positive tumor cells and staining intensity. The percentage of stained cells was categorized as <25% (0), 25–50% (1), or >50% (2), while intensity was graded as absent (0), weak (1), moderate (2), or strong (3). For statistical evaluation, tumors demonstrating any specific staining were classified as positive. Immunostaining was performed using AGGF-1 polyclonal concentrate, 0.1 mL (1:400) and ANTIBDIESONLINE ABIN6272953-200UL, AGGF1/VG5Q [Polyclonal], C. Liq. 0.2ml (1:50-200), and ROCHE/Ventana R 05269806001 Ultraview Universal DAB Detection Kit.

Patient data including demographics, clinicopathological features, outcomes, radiological responses, and laboratory parameters were obtained from medical oncology outpatient clinic files, hospital medical records, and electronic medical records.

The study was approved by the institutional ethics committee of the Sakarya University Faculty of Medicine (approval number: 23.11.2018-71522473/050.01.04) and was conducted in alignment with the principles of the Declaration of Helsinki. Due to the retrospective design utilizing archival pathology specimens, the ethics committee waived the necessity for individual informed consent.

Statistical Analysis

Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies and percentages. Group comparisons were conducted

using appropriate statistical tests according to data distribution. Survival outcomes were analyzed using Cox regression models. A p value <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were utilized to ascertain the parameters influencing PFS and OS.

Results

A total of 67 patients were included in the study. The median age was 65 years (range: 35-86). KRAS mutations were identified in 61.2% (n= 41) of the patients. BRAF mutation status was available in 4 patients within the cohort; 3 patients had wild-type BRAF, and 1 patient harbored a BRAF mutation. All patients received bevacizumab as part of the initial treatment for metastatic disease. AGGF-1 staining was positive in 49.25% (n=33) patients. Forty patients had an ECOG performance status of 0, while 27 (40.3%) patients had a status of 1. Table 1 summarizes the demographic and clinical characteristics of patients with positive and negative AGGF-1 expression.

Patients were divided into three groups based on the proportion of AGGF-1 staining. Thirty-four patients had no staining (<25%), eight patients had focal staining (25-50%), and twenty-five patients had diffuse staining (>50%). Patients were also categorized into four groups according to the intensity of AGGF-1 staining. Thirty-four patients showed absent staining intensity (0), 18 patients had weak intensity (1), 13 patients had moderate intensity (2), and two patients exhibited strong (3) intensity.

The median OS was 19.8 months (95% CI, 15.52-24.07), and the median PFS was 5.6 months (95% CI, 4.82-6.51) for all patients. No significant differences were found when patients were compared according to AGGF-1 staining status. The median OS was 20 months (95% CI, 13.97-25.97) in the AGGF-1-negative group and 18.6 months (95% CI, 12.07-25.26) in the AGGF-1-positive group. The median PFS was 5.8 months (95% CI, 5.58-6.15) in the AGGF-1-negative group and 4.4 months (95% CI, 3.26-5.66) in the AGGF-1-positive group. No statistically significant differences were observed between the two groups regarding AGGF-1 staining status (p=0.78 and p=0.20, respectively) (Fig. 1a, 1b).

Cox regression analysis was employed to examine the factors influencing PFS and OS (Table 2). Variables with p <0.10 in the univariate analysis were subsequently incorporated into the multivariate Cox regression model.

In the multivariate Cox regression analysis for PFS, staining intensity, age, and primary tumor location were included in the model. Overall, staining intensity showed a significant association with PFS (overall p=0.009); however, when compared with the reference category, none of the individual staining intensity levels reached statistical significance. Age was not independently associated with PFS (HR=0.98, 95% CI: 0.96–1.01; p=0.163). The location of primary tumor was an independent prognostic factor for PFS, with a significant disparity noted between left- and right-sided tumors (HR=2.55, 95% CI: 1.33–4.88; p=0.005).

Table 1. Demographic and clinical characteristics of the AGGF-1 expression positive and negative patients

Variable	AGGF-1 expression status		p
	Negative (n=34)	Positive (n=33)	
Age, yr (min-max)			
Median	65 (37-79)	64 (35-86)	0.744
Gender, n (%)			
Female	9 (26.5)	10 (30.3)	0.728
Male	25 (73.5)	23 (69.7)	
Location of primary tumor, n (%)			
Right	12 (35.3)	10 (30.3)	0.664
Left	22 (64.7)	23 (69.7)	
Primary tumor operation status, n (%)			
Yes	29 (85.3)	24 (72.7)	0.206
No	5 (14.7)	9 (27.3)	
Mutation status, n (%)			
RAS mutant	21 (61.8)	22 (66.7)	0.508
RAS wild	8 (23.5)	9 (27.3)	
Unknown	5 (14.7)	2 (6.1)	
Metastasis status, n (%)			
Recurrence	16 (47.1)	7 (21.2)	0.026
De novo	18 (52.9)	26 (78.8)	
Liver metastasis, n (%)			
Yes	23 (67.6)	24 (72.7)	0.650
No	11 (32.4)	9 (27.3)	
Lung metastasis, n (%)			
Yes	10 (29.4)	4 (12.1)	0.082
No	24 (70.6)	29 (87.9)	
Peritoneal carcinomatosis, n (%)			
Yes	9 (26.5)	8 (24.2)	0.834
No	25 (73.5)	25 (75.8)	
First Line treatment, n (%)			
FOLFOX/XELOX+B	19 (57.6)	21 (70.0)	0.306
FOLFIRI+B	14 (42.4)	9 (30.0)	
Best response for first line treatment, n (%)			
Complete	4 (11.8)	2 (6.1)	0.288
Partial+stable	24 (70.6)	20 (60.6)	
Progression	6 (17.6)	11 (33.3)	

AGGF-1: Angiogenic factor with G-patch and FHA domain 1; yr: Year; RAS: Rat sarcoma viral oncogene homolog; Wild: Wild-type; FOLFOX+B: 5-fluorouracil, leucovorin and oxaliplatin+ bevacizumab; FOLFIRI+ B: 5-fluorouracil, leucovorin and irinotecan+ bevacizumab.

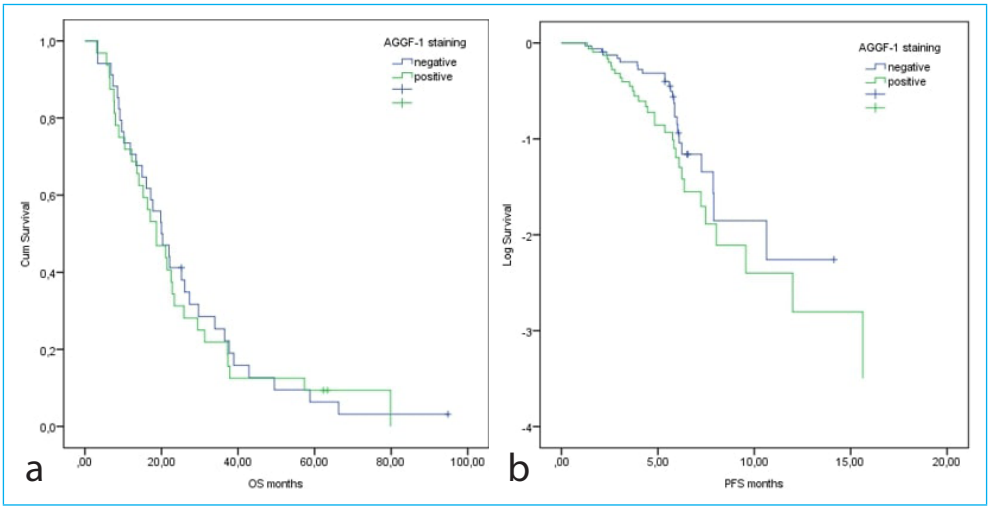

Figure 1. Kaplan-Meier curves comparing overall survival (OS) (A) and progression-free survival (PFS) (B) between the AGGF-1-positive group and the AGGF-1- negative group.

For OS, multivariate Cox regression analysis identified metastasectomy as an independent protective factor (HR=0.474, 95% CI: 0.231–0.974; p=0.042). Conversely, primary tumor location remained an adverse prognostic factor for OS (HR=2.470, 95% CI: 1.298–4.699; p=0.006). In addition, baseline CEA level at diagnosis was independently associated with poorer OS (HR=1.001, 95% CI: 1.000–1.001; p=0.001).

Table 2. Univariate cox regression analysis of PFS and OS in patients treated with first-line bevacizumab plus 5-FU–based chemotherapy

		PFS		OS	
Variable	**Category**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Staining status (ref: positive)	Negative vs. positive	0.72 (0.42–1.20)	0.206	0.93 (0.56-1.53)	0.780
Staining proportion (ref: absent)	Overall	-	0.198	--	0.635
	Focal vs. absent	0.69 (0.40–1.22)		1.01 (0.59-1.75)	
	Diffuse vs. absent	0.90 (0.40–2.01)		1.45 (0.64-3.30)	
Staining intensity (ref: absent)	Overall	-	0.032	--	0.982
	Weak vs. absent	0.38 (0.09–1.66)		1.13 (0.27-4.78)	
	Moderate vs. absent	0.38 (0.08–1.71)		1.25 (0.28-5.53)	
	Strong vs. absent	0.95 (0.21–4.28)		1.22 (0.27-5.50)	
Gender (ref: male)	Female vs. male	1.42 (0.79–2.52)	0.238	1.07 (0.61-1.88)	0.797
Age	Continuous	0.98 (0.95–0.99)	0.045	1.02 (0.99-1.04)	0.113
Metastasis status (ref: multiple)	Oligo vs. multiple	0.95 (0.56–1.59)	0.835	0.69 (0.41-1.17)	0.175
Location of primary tumor (ref: right)	Left vs. right	0.41 (0.23–0.74)	0.003	1.78 (1.03-3.06)	0.037
Primary tumor operation status (ref: present)	Absent vs. present	1.29 (0.65–2.54)	0.462	0.90 (0.47-1.70)	0.747
CEA level	Continuous	1.00 (1.00-1.00)	0.194	1.00 (1.00-1.00)	0.013
CA 19-9 level	Continuous	1.00 (1.00-1.00)	0.385	1.00 (1.00-1.00)	0.113
Liver metastasis (ref: present)	Absent vs. present	0.91 (0.51–1.62)	0.750	1.09 (0.63-1.90)	0.740
Lung metastasis (ref: present)	Absent vs. present	0.95 (0.51–1.77)	0.872	1.24 (0.68-2.28)	0.476
Peritoneal carcinomatosis (ref: present)	Absent vs. present	1.17 (0.65-2.12)	0.601	1.50 (0.83-2.71)	0.171
Metastasectomy (ref: present)	Absent vs. present	0.80 (0.44-1.46)	0.478	0.37 (0.19-0.70)	0.003
First line therapy (ref:oxaliplatin)	İrinotecan vs. oxaliplatin	1.01 (0.58-1.75)	0.956	0.69 (0.41-1.15)	0.161

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; Ref: Reference; Vs: Versus; 5-FU: 5-fluorouracil; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; Oligo: Oligometastatic disease; Multiple: Multiple metastases.

Discussion

Colorectal cancer is a complex disease consisting of several molecular subgroups, potentially resulting in variations in therapy response.[1,3] Numerous molecules secreted by the tumor and its microenvironment (growth factors, cytokines, etc.) play critical roles in tumor biology, proliferation, and metastasis, and ultimately influence treatment outcomes. Angiogenesis is essential for tumorigenesis.[12]

This is the first investigation of the correlation between AGGF-1 expression and treatment response in patients with mCRC receiving first-line bevacizumab-combined chemotherapy. Despite the widespread integration of anti-angiogenic agents into mCRC treatment algorithms, no clinically established biomarker currently exists to accurately predict therapeutic benefit. Given the role of AGGF-1 in tumor angiogenesis, we evaluated whether AGGF-1 tumor staining is associated with clinical outcomes.

An angiogenic molecule, AGGF-1, has been reported to be highly expressed in gastrointestinal cancer types—hepatocelluler carcinoma, gastric cancer—and to be associated with poor prognosis.[7,8] However, to date, no studies in the literature have demonstrated that AGGF-1 functions as a predictive biomarker. In patients with AGGF-1 expression positive, both OS (20 vs. 18.6 months) and PFS (5.8 vs. 4.4 months) were shorter, consistent with a poorer prognosis. However, these differences did not reach statistical significance. Furthermore, AGGF-1 staining intensity was significantly associated with progression-free survival in both univariate and multivariate Cox regression analyses, indicating that staining intensity can be an independent prognostic factor for PFS (overall p=0.009). However, when individual staining intensity levels were compared with the reference category, none reached statistical significance, likely due to limited statistical power and wide confidence intervals. This finding likely reflects limited statistical power and wide confidence intervals rather than the absence of a true biological effect. Importantly, the observed pattern suggests a non-linear relationship between AGGF-1 expression level and treatment response, indicating that moderate levels of expression may be more clinically relevant than extreme expression levels.

Yao et al.[8] investigated AGGF-1 expression in gastric cancer patients using IHC and showed that AGGF-1 expression was significantly associated with lymph node metastasis, invasion depth, and TNM stage. They also observed a significant positive correlation between VEGF and AGGF-1 expression in gastric cancer samples (p=0.017). In our study, we found higher AGGF-1 expression in de novo metastatic patients compared to recurrent metastatic patients (p=0.026). These findings point to an aggressive biology and AGGF-1 expression may facilitate metastasis in CRCs. Validation in larger, prospectively designed cohorts will be essential to better define the clinical significance of AGGF-1 expression.

Anti-VEGF therapy, commonly used in mCRC, has shown better outcomes in patients with right-sided tumors, MSI, and good PS. Although it is theoretically suggested that VEGF levels may be related to treatment response, no prospective clinical data have yet confirmed this. Some retrospective studies support this relationship, but they have not demonstrated statistically significant results.[13–15]. In current oncology practice, the clinical importance of KRAS point mutations (G12C, G12D, etc.) is increasing. Inside the cell membrane mechanisms have become a therapeutic target with KRAS mutation-specific inhibitors (sotarasib, adagrasib, etc.).[2,16] In these intracellular targeted therapies, combination with targeted therapies that act on the cell membrane and microenvironment (immune checkpoint inhibitors, EGFR) is being evaluated to break resistance.[16–18] In our study, the first-line treatment responses were worse in patients with AGGF-1 expression despite receiving anti-VEGF therapy. The risk of early progression was increased two-fold (33.3% vs. 17.6%) in AGGF-1 positive group. The AGGF-1 molecule may represent a strong potential target for future therapies.

Conclusion

Nonetheless, numerous shortcomings of this study require acknowledgment. This study employed a retrospective methodology and had a somewhat small sample size. Due to the predominance of immunohistochemically negative cases, semi-quantitative evaluation of staining extent and intensity was not feasible for incorporation into a composite scoring system; therefore, a binary classification approach was applied.

Second, AGGF-1 protein expression was assessed solely by immunohistochemistry in archived tissue samples, and gene expression levels were not evaluated. Although staining intensity and extent may be influenced by specimen quality and interobserver variability, future studies with larger cohorts and more objective molecular techniques, such as polymerase chain reaction–based assays, are warranted to standardize positivity thresholds.

In addition, MSI data were unavailable, and BRAF mutation status was available only for a limited number of patients, precluding the incorporation of molecular characteristics into survival analyses.

Finally, the precise molecular mechanisms underlying the role of AGGF-1 in colorectal cancer angiogenesis remain to be elucidated, and prospective studies integrating genomic and proteomic analyses are needed to validate AGGF-1 as a predictive biomarker.

Disclosures

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Sakarya (Approval no: 71522473/050.01.04, Date:23.11.2018).

Informed Consent: Due to the retrospective design utilizing archival pathology specimens, the ethics committee waived the necessity for individual informed consent.

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