RESEARCH COMMUNICATION

Prognostic Factors for Overall Survival in Patients With Metastatic Colorectal Carcinoma Treated With Vascular Endothelial Growth Factor-Targeting Agents

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Abstract

Objective: Angiogenesis represents a key element in the pathogenesis of malignancy. There are no robust data on prognostic factors for overall survival (OS) in patients with metastatic colorectal cancer treated with vascular endothelial growth factor (VEGF)-targeted therapy. The present study was conducted to establish a prognostic model for patients using an oxaliplatin-based or irinotecan-based chemotherapy plus bevacizumab in metastatic colorectal cancer. Methods: Baseline characteristics and outcomes on 170 patients treated with FOLFIRI or XELOX plus anti-VEGF therapy-naïve metastatic colorectal cancer were collected from three Turkey cancer centers. Cox proportional hazards regression was used to identify independent prognostic factors for OS. Results: The median OS for the whole cohort was 19 months (95% CI, 14.3 to 23.6 months). Three of the seven adverse prognostic factors according to the Anatolian Society of Medical Oncology (ASMO) were independent predictors of short survival: serum lactate dehydrogenase (LDH) greater than the upper limit of normal (ULN; p<0.001); neutrophils greater than the ULN (p<0.0014); and progression free survival (PFS) less than 6 months (p =0.001). Conclusion: Serum LDH and neutrophil levels were the main prognostic factors in predicting survival, followed by PFS. This model validates incorporation of components of the ASMO model into patient care and clinical trials that use VEGF-targeting agents.

Keywords: Vascular endothelial growth factor - bevacizumab - prognostic factors - metastatic colorectal cancer

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Introduction

Unresectable metastatic colorectal cancer (CRC) is generally not curable with current treatment modalities. Management focuses on palliation and control of symptoms, control of tumor growth, and attempts to lengthen progression-free and overall survival. Given the palliative nature of such treatments, extreme care must be taken to adequately assess each individual' s potential for both benefit and harm from chemotherapy. This is best achieved by using well-established combination doublets (ie, FOLFOX, XELOX, or FOLFIRI) as the chemotherapy backbone, which would then only require one additional step to have all three active agents included in the treatment algorithm for second-line therapy (eg, FOLFOX followed by FOLFIRI, or FOLFIRI followed by FOLFOX).

Bevacizumab is a humanized monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby substantially reducing the amount of circulating ligand and thus preventing receptor activation (Ferrara et al., 2004; Ferrara, 2004).

In this era of VEGF-targeted therapies, contemporary prognostic variables are required to better stratify patients in clinical trials, to provide relevant clinical information to patients receiving therapy, and to facilitate risk-directed treatment selection in clinical practice. Although there are currently no validated biomarkers for clinically assessing the efficacy of or selecting patients who will respond to antiangiogenic therapies, a number of candidate markers including tissue, imaging, and circulating biomarkers are emerging that need to be prospectively validated (Kerbel et al., 2004; Mancuso et al., 2006).

A retrospective, multicenter study to include consecutive patient series from three different oncology treatment centers in the Turkey. The purpose of this study was to create a simple clinical-prediction model that would be applicable to the general population of patients with

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metastatic colorectal cancer treated with chemotherapy plus VEGF-targeted therapy.

Materials and Methods

Patient Population

One hundred and seventy patients with metastatic CRC treated with FOLFIRI/XELOX/IFL plus bevacizumab between August 2006 to July 2010 were included in this study. Patient inclusion criteria comprised a diagnosis of metastatic CRC of adenocarcinoma with no prior anti-VEGF therapy. Patients who received as second-line treatment also were included. All patients were unresectable liver metastases at initial consultation with regard to their primary tumors. The patients who had hepatic resection and local ablative therapy or chemoembolization therapy were excluded. Patients with CNS metastases, exclusive bone metastasis, and other serious nonmalignant disease were excluded . Laboratory values were standardized against institutional the upper limit of normal (ULN) and the lower limit of normal (LLN) values when appropriate.

Statistical Analyses

Progression-free survival was defined as the time interval from randomization to first disease progression or death from any cause if disease progression did not occur. Overall survival (OS) was defined as the time interval from randomization to death from any cause. Statistical analysis was made using computer software (SPSS version 17.0, SPSS Inc. Chicago, IL, USA). Kaplan–Meier curves were used to summarize overall survival and groups were compared by the log-rank test for categorical factors and Cox's proportional hazards model for continuous factors, by univariate analysis. All prognostic variables determined to be significant in univariate analysis were included in multivariate analysis using Cox's proportional hazards model. Data were expressed as "mean (standard deviation; SD)", minimum-maximum, percent (%) and 95% CI, where appropriate. $p<0.05$ was considered statistically significant. The disease duration and other variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogrov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. As both parameters were normally distributed, the correlation coefficients and their significance were calculated using the Pearson test.

Results

Patient Characteristics and Outcomes

Baseline characteristics are presented in Table 1. Prior adjuvant chemotherapy with oxaliplatin or 5-FU/LV was given 67 patients (39.4%). One hundred fourty nine patients (77.2%) had first line anti-VEGF therapy, and 44 patients (22.8%) had second-line anti-VEGF therapy. The median OS for the entire cohort of 170 patients was 18 months (95% CI, 14.2 to 21.7 months; Figure 1).

Univariable Analysis

All 14 potential predictive covariates with their univariable analyses are presented in Table 2. Clinical features that were significantly associated with poor OS included: a PFS less than 6 month, performance status (PS) 1 and primitive tumor localization. Laboratory features demonstrating association wereanemia, neutrophilia, thrombocytosis, elevated CEA and elevated LDH. Of note, there were no differences in OS with patients receiving VEGF-targeted therapy first- or second-line (p= 0.060).

Table 1. Univariate Analysis of Patient Demographic and Clinical Characteristics and Overall Survival

Parameter	No. of Patients	Median Overall Survival (months)	Univariate analysis p-value
Age, years			0.234
≥60	50	18	
<60	120	19	
Sex			0.634
Male	94	16	
Female	76	22	
PS			0.001
0	100	23	
1	70	14	
Treatment			0.12
First-line anti-VEGF	132	23	
Second-line anti-VEGF	38	16	
Anemia			0.034
Yes	25	15	
No	145	19	
Neutrophilia			0.033
Yes	18	9	
No	152	20	
Thrombocytosis			0.008
Yes	43	16	
No	127	22	
Elevated LDH			0.001
Yes	69	15	
No	99	31	
Time to metastasis			0.367
Metachronous	77	17	
Synchronous	93	24	
Elevated CEA			0.002
Yes	118	17	
No	49	31	
PFS			0.001
≥6 ay	112	27	
<6ay	58	9	
BMI			0.613
<25	76	19	
25-30	67	18	
>30	24	29	
Primary tumor			0.14
Intact	42	15	
Non-intact	128	19	
Primitive tumor			0.05
Colon	100	22	
Rectum	70	15	

* 'Abbreviations: CEA, carcino-embryonic antigen; LDH, lactate dehyrogenase; PS, performance status; BMI, Body-mass index; PFS, Progression free survival

Multivariable Analysis

In the resulting Cox proportional hazards model (Table

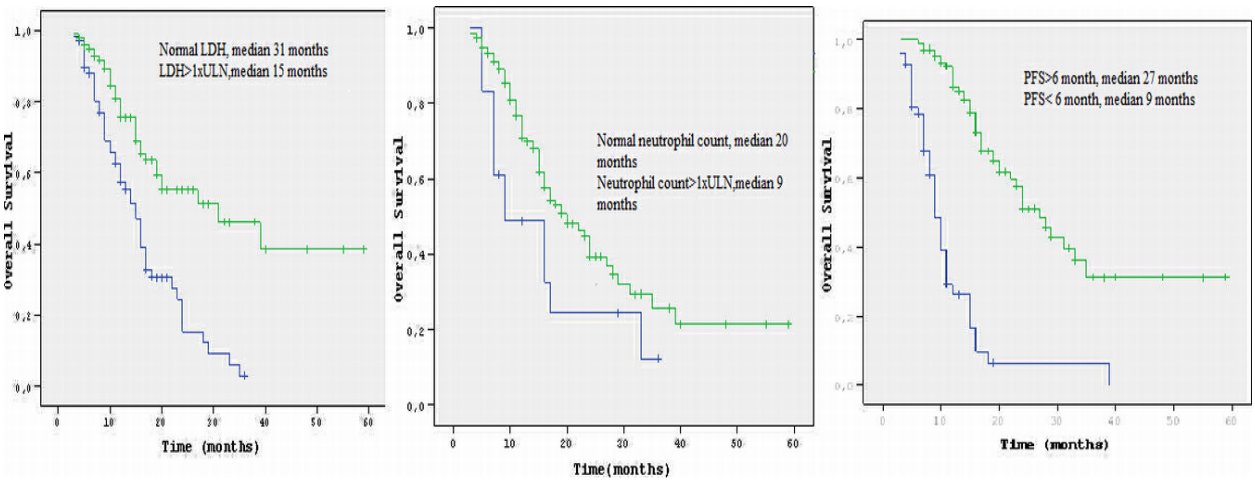

Figure 1. Overall Survival Probability According to Time After Therapy Initiation.

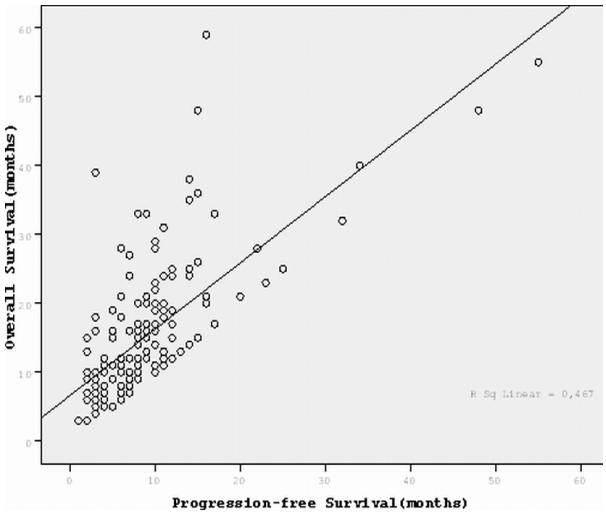

Figure 2. Scatter Plot of Progression-Free Survival (PFS) with Respect to Overall Survival (Pearson Correlation r:0.683 p=0.001).

3), three of the eight adverse prognostic factors —absolute neutrophil count greater than ULN (p= .008), serum LDH greater than the ULN (p =.0001) and PFS less than 6 moths (p=.0001) were independent predictors of short survival. The Kaplan-Meier curves depicting these three risk categories are shown in Figure 2.A data set from an our trial was analyzed to assess whether progression-free survival (PFS) could be used as a predictor of overall survival (OS) and to investigate the dependence between PFS and OS in patients metastatic CRC. There was a good relation between PFS and OS (Pearson Correlation r: 0.683 p=0.001 Figure 3).

Discussion

VEGF-targeted therapies when combined with cytotoxic chemotherapy have created a new environment for clinical trials development and patient care in patients with metastatic colorectal cancer. Antiangiogenic therapy has created a need to develop effective biomarkers to assess the activity of these inhibitors. Surrogate markers of tumor angiogenesis activity are important to guide clinical development of these agents and to select patients most likely to benefit from this approach. We investigated the

Table 2. Multivariable Analysis and Final Model

Parameter	Multivariate analysis				
	No.of patients	Median overall survival (months)	OR	95% CI	p-value
Neutrophilia					0.014
No	152	20	1		
Yes	18	9	2.18	1.169-4.065	
Elevated LDH					0.001
No	69	31	1		
Yes	99	15	2.273	1.440-3.588	
PFS					0.001
≥6 month	112	27	1		
<6 month	58	9	6.117	3.814-9.809	

* 'LDH, lactate dehyrogenase; PFS, Progression free

effect of various surrogate markers on survival among the patients with metastatic colcorectal cancer. Current indicators cannot predict which patients will develop resistance or when resistance will develop (Grothey et al., 2008).

The final model described in this study is composed of three clinical and five laboratory values that are readily available and that have been demonstrated to be associated with adverse outcomes. Clinical features that were significantly associated with poor OS included; a PFS less than 6 months, performance status (PS) 1 and primitive tumor localization. Laboratory features that were associated with poor OS included anemia, neutrophilia, thrombocytosis, elevated CEA and elevated LDH .In the resulting Cox proportional hazards model , four of the eight adverse prognostic factors —absolute neutrophil count greater than ULN (p = 0.014), serum LDH greater than the ULN (p =0.001) and PFS less than 6 months (P=0.001) were independent predictors of short survival.

LDH is an enzyme detectable in serum that is often elevated in multiple cancers including colorectal cancer, has prognostic importance and is regulated by the PI3 kinase/Akt/mTOR pathway and tumor hypoxia/necrosis. In this study, LDH was the most important prognostic factor, with a twofold risk for mortality in the case of increased level at baseline. LDH has been previously identified as a prognostic factor in colorectal cancer

(Kemeny et al., 1983; de Gramont et al., 2000; Saltz et al., 2000; Tournigand et al., 2004:2006) and other tumor localizations (Coiffier et al., 1991; Dimopoulos et al., 1991; Tas et al., 2001; Nisman et al., 2003).

Of note, LDH has also been identified as a potential predictive factor for a vascular endothelial growth factor inhibitor and chemotherapy combination in patients with metastatic colorectal cancer (Hecht et., 2005).

Neutrophilia (Donskov et al., 2006) and thrombocytosis (Hollen et al., 1992; Suppiah et., 2006) maybe markers of inflammation related to the overproduction of cytokines as a result of increasing tumor burden or aggressive tumor biology. Only one single-arm study that has examined the effect of peripheral blood neutrophil counts on the efficacy of several anti-VEGF drugs in metastatic renal cell carcinoma (Heng et al; 2009). Our data show that a neutrophil count greater than the upper limit of the normal range is associated with worse outcome after treatment with chemotherapy plus bevacizumab. After LDH, neutrophil count was the second strongest prognostic factor associated with OS with a twofold risk for mortality.

The association between highly elevated serum tumor marker concentration and metastases and poor prognosis was also discovered through CEA studies. However, clinical decisions regarding management of disease cannot be based on CEA levels alone. As the liver metabolizes CEA, liver damage can impair CEA clearance and lead to increased levels in the blood circulation. CEA level at baseline (p=0.002) and performance status (PS) 1 (p=0.001) and primitive tumor localization (p=0.05) were significant in univariate analysis but not prognostic factors in the multivariate analysis. Sex, age, synchronous disease and body-mass index were not prognostic factors in the univariate analysis. In stage IV colorectal cancer with unresectable metastatic disease, the role of resection of the primary tumour remains unclear. Patients were randomly assigned to stage IV colorectal cancer with unresectable metastases with asymptomatic intact colon (non-surgery group) and whose primary tumors resected. Median overall survival was 15 months for non-surgery group (95%Cl, 12.8 to 17.1 months) and was 19 months for surgery group (95 % Cl, 13.8 to 24.1 months; p=0.140).

Progression free-survival (PFS) has been used as a clinical trial endpoint evaluating the efficacy of novel agents in metastatic CRC, and has led to the approval by the FDA of VEGF targeted therapeutics. This approach is attractive as a major impact on survival by first line and beyond therapies with emerging active agents. PFS has also been proposed as a potential surrogate for OS in patients with advanced colorectal (Buyse et al., 2007), breast (Burzykowski et al., 2008) , prostate (Collette et al., 2005) and ovarian cancer (. Burzykowski et al., 2001). The correlation between PFS and OS was acceptably high (suggesting good individual-level surrogacy) in ovarian and colorectal cancer, as indicated by squared correlation coefficients of 0.70 and 0.82, respectively . The squared correlation coefficient represents the proportion of variance in the clinical endpoint explained by the surrogate. In contrast, the correlation between PFS and OS was unacceptably low (suggesting poor individual-level surrogacy) in breast cancer, as indicated by a squared correlation coefficient of 0.47 . In the resulting Cox proportional hazards model, one of the three adverse prognostic factors including PFS (6 months or less than 6 months; p=0.000), were determined to be independent predictors of short survival and there was a good relation between PFS and OS (Pearson Correlation r: 0.683 p=0.001).

The limitations to this study include that this is a retrospective analysis that has the associated issues of potential selection bias, incomplete data collection. Attempts to address these concerns were made and included the use of consecutive patient sampling to reduce patient selection bias and several efforts to obtain complete patient information from medical records, provincial registries, and physician offices. A dditionally, this patient population was treated with chemotherapy plus bevacizumab in either the first- or second-line setting. This is in keeping with our data on overall survival, which show that OS is unaffected by targeted therapy administered as first- or second-line (median OS, 24 months v 17 months; P=0.060).

In conclusion; better discrimination is needed to improve therapeutic decisions. A combination model of prognostic and predictive factors could lead to better selection of patients before initiating treatment. If validated, this simple prognostic model could help identify which subgroup of patients should receive antiangiogenic therapy and lead the way to possible future tailoring of individualized antiangiogenic therapy.

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