Serum Alkaline Phosphatase Level as a Prognostic Tool in Colorectal Cancer: A Study of 105 patients

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ABSTRACT

Background: Serum alkaline phosphotase (ALP) levels are frequently elevated in patients with metastatic colorectal cancer (CRC). However, the significance of ALP in terms of detecting hepatic metastasis or prognosis is not well established.

Materials and Methods: Medical records of patients with CRC seen at University of Alabama at Birmingham (UAB) (1998-2002) were reviewed and statistical analysis was done to evaluate the significance of ALP as a prognostic tool. The normal range for ALP was quantified at 39 U/L to 117 U/L. Change in ALP levels over time (defined as time interval between two cycles; such as 4 weeks for Mayo regimen, 8 weeks for Roswell Park regimen and 6 weeks for IFL regimen) was categorized as large (120+ U/L), medium (20-119 U/L), and minimal (< 20 U/L).

Results: A total of 105 patients with eligible medical records were identified (Mean age: 59 yrs; 53% male; Staging: II: 43 patients, III: 31 patients, IV: 32 patients). Increasing ALP levels correlated with increasing stage (Mean: I = 116, II = 219, III = 302; $P = 0.0003$). ALP levels were elevated in 74% of patients with liver metastases (Mean, 290) and in 33% without liver metastases (Mean, 122) ($P = 0.001$). Patients with elevated ALP levels at the most recent time of progression were 5.7 (95% CI, 2.4-13.3) times more likely to have a liver metastases compared to patients with normal levels. Additionally, patients with elevated ALP levels at their most recent visit were 4.2 (95% CI, 1.7-10.7) times more likely to have a worse prognosis compared to patients with normal levels. However, after controlling for the effects of liver metastases, the association between elevated levels and prognosis was no longer significant. After

controlling for the effects of age, sex, and liver metastases, large changes in AP levels were associated with a 4.4 (95% CI, 1.0-19.1) times greater odds of having a worse prognosis compared to patients with a minimal change. Patients with an ALP level greater than 160 were 12 (95% CI, 4.3-33.3) times more likely to have liver metastases than patients with an ALP level of less than 160. Mean CEA level was 78 for patients without liver metastases and 308 for patients with liver metastases. CEA levels were compared against ALP in a random sample of 18 patients, which revealed a correlation between increasing levels of CEA (.002) with increasing levels of ALP.

Conclusion: Instead of the upper normal limit for ALP, our data shows that using an ALP cutoff of 160 U/L increases the sensitivity of liver metastases detection. Also, a change in ALP levels of greater than 120 U/L over four-to-six weeks may be indicative of disease progression. Monitoring ALP is a simple, low cost, and relatively sensitive screening tool. Prospective studies involving evaluation of ALP in addition to CEA in patients with CRC is indicated.

INTRODUCTION

Alkaline phosphatase (ALP) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate.[1] Like other enzymes, this enzyme has many isoenzymes. In healthy adults, this enzyme is mainly derived from the liver, bones, and in lesser amounts from intestines, placenta, kidneys, and leukocytes.[2] An increase in serum ALP levels is frequently associated with a variety of diseases, such as extrahepatic bile obstruction, intrahepatic cholestasis, infiltrative liver disease, and hepatitis. In general, the elevation of ALP less than three times the normal level is considered nonspecific and insufficient to provide a definite diagnosis.[3] Markedly elevated serum ALP, hyperalkalinephosphatasemia, is seen predominantly with more specific disorders, including, malignant biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, hepatic lymphoma, and sarcoidosis.[4] On the other hand, according to a recent study,[5] sepsis and malignant obstruction are identified as common causes of hyperalkalinephosphatasemia, whereas diffuse liver metastasis, as well as a number of benign disorders, are relatively less common causes of hyperalkalinephosphatasemia.

Serum ALP levels are frequently elevated in patients with metastatic colorectal cancer (CRC). There are anecdotal reports and small studies suggesting that the elevated ALP can aid in detecting metastatic liver disease. This is an important issue as biological detection of liver metastases represents an important factor in the prognosis of patients with CRC.

To evaluate the role of ALP as a predictor of liver disease and a prognostic factor, a review was made of medical records of individuals with colorectal cancer treated during a period of 4 years.

MATERIALS AND METHODS

Retrospective review of all patients diagnosed and/or treated for the colon and rectal cancer (International Classification of Diseases for Oncology code, 153 and 154) first diagnosed from January 1998 to December 2001 at the University of Alabama at Birmingham (UAB) was conducted. A total of 155 patients were identified with a final diagnosis of colorectal cancer, whether by surgical biopsy or by autopsy. A total of 105 patients with eligible medical records were found for final analysis. Patients presenting with only a clinical

Table 1. Demographic Data (Male vs Female)*

Variable	All	Male	Female	*P* value
N	105	55	50	
Age: Mean	58.8	60.7	56.5	.10
Median	60	62	57	
Stage: II	43	21 (49%)	22 (51%)	
III	31	18 (58%)	13 (42%)	
IV	31	16 (52%)	15 (48%)	
Alk Phos at Dx:				
Mean	98.1	106.7	88.0	.10
Normal	81	41 (51%)	40 (49%)	
Elevated	17	12 (70.5%)	5 (29.5%)	
Alk Phos Final:				
Mean	201.8	201.8	201.8	.99
Normal	49	28 (57%)	21 (43%)	
Elevated	54	27 (50%)	27 (50%)	
Prognosis:				
More Favorable	29	17 (57%)	13 (43%)	
Stable	23	14 (61%)	9 (39%)	
Less Favorable	32	18 (51%)	17 (49%)	
Liver Metastasis	49	29 (59%)	20 (41%)	
CEA at Dx	15	73.8	17.6	.30
CEA final	17	290.3	143.5	.42
CEA at Dx	14	3.2	17.6	.25
CEA final	14	10.9	61.7	.10

*P value denotes male to female differences. Percents are expressed across rows. Alk phos indicates alkaline phosphatase level; dx, diagnosis; and CEA, carcinoembryonic antigen level.

impression of cancer, but who came neither for laparatomy or autopsy, were excluded from the analysis. If a patient lacked tissue confirmation, an in-depth medical chart review was conducted to determine the accuracy of diagnosis. Exclusion was made in cases of patients who have bone involvements with malignancy, patients with other concurrent malignancies, and HIV seropositive patients. Patients who did not die at UAB hospitals were followed-up through contact with tumor registry, their private surgeons, and their relatives. Patients whose missing parameters could not be found were excluded from the analysis. Extent of disease and tumor grade was based on the best available data using a modification of the American Joint Committee on Cancer (AJCC) TNM classification system.

The data were recorded including their age, sex, final diagnosis, stage, liver disease, ALP, and CEA. The normal range for ALP was quantified at 39 U/L to 117 U/L. Change in ALP levels over time (defined as time interval between two cycles; such as 4 weeks for Mayo regimen, 8 weeks for Roswell Park regimen and 6 weeks for IFL regimen) was categorized as large (120+ U/L), medium (20-119 U/L), and minimal (< 20 U/L). Prognosis was defined as favorable for patients surviving at 12

Table 2. Descriptive Data (Stage Differences)*

Variable	All	Stage II	Stage III	Stage IV	*P* value
N	105	43	31	31	
Age: Mean	58.7	58.6	60.9	56.5	.57
Median	60	60	62	57	
Male		55	21 (38%)	18 (33%)	16 (29%)
Female	50	22 (44%)	13 (26%)	15 (30%)	
Alk Phos at Dx:					
Mean	98.1	94.3	101.7	100.0	.30
Normal	81	37 (45.7%)	23 (28.4%)	21 (25.9%)	
Elevated	17	4 (24%)	7 (41%)	6 (35%)	
Alk Phos Final:					
Mean	201.8	115.5	218.9	302.2	.0003
Normal	49	26 (53%)	11 (22.5%)	12 (24.5%)	
Elevated	54	16 (30%)	19 (35%)	19 (35%)	
Prognosis:					
More Favorable	30	17 (56.6%)	8 (26.6%)	5 (16.6%)	
Stable	23	11 (48%)	8 (35%)	4 (17%)	
Less Favorable	35	8 (23%)	11 (31%)	16 (46%)	

*P value denotes Spearman Correlation for stages across rows. Percents are expressed across rows. Alk phos indicates alkaline phosphatase level; and dx, diagnosis.

months versus unfavorable for patients dying before 12 months from the day of diagnosis. Descriptive statistics were used in analyzing the patient characteristics and laboratory parameters for each group. In addition, unpaired Student *t* test was used to assess group differences, where appropriate. Independence was tested by Chi square test. A statistical significant difference was accepted as *P* value less than 0.05. All the statistical analyses in this study were made using SPSS 7.0 for Windows Program.

RESULTS

Among 155 patients identified, a total of 105 patients with eligible medical records were found. They were 55 male and 50 female patients with mean age of 58.8 years and median age of 60 years (Table 1). Forty-three patients were diagnosed (at the time of initial diagnosis) at stage II, 31 patients at stage III, and 32 patients at stage IV. There is not a significant difference in age across stage; however, the mean age is lower among the stage IV patients. There is clearly a difference in mean ALP level at time of diagnosis (98 U/L) compared to final levels (defined as the latest levels) (202 U/L). This remained prevalent after the exclusion of 4 outliers. A greater percentage of females changed from normal to elevated ALP levels. Overall, the mean ALP level at the time of diagnosis was 98.1 U/L, with elevated level in 18% of patients and normal in 82% of patients. Mean ALP level at the latest evaluation was 202 U/L, with elevated levels in 55% of patients and normal in 45% of patients. According to the stage of colorectal cancer, the ALP levels were: Stage II (Mean, 94 U/L; elevated in 24%; normal in 48%), Stage III (Mean, 108; elevated in 41%; normal in 29%), and Stage IV (Mean, 100; elevated in 26%; normal in 35%) (Table 2). ALP level at the latest evaluation in patients initially diagnoses at different

Table 3. ALP and Liver Metastases*

Variable	Liver Metastases	No. Liver Metastases	*P* value
N	49	56	
Mean Age	58.9	58.5	.86
Alk Phos at Dx	110.4	87.7	.05
Alk Phos Final	289.6	122.1	.001
Alk Phos Final (Without 4 Outliers)	217.5	103.7	.0001
Prognosis:	N	N	.0001†
More Favorable	7	23	
Stable	7	16	
Less Favorable	28	7	

*Alk phos indicates alkaline phosphatase level; and dx, diagnosis. †ANOVA with recoded prognostic values (1 indicates more favorable; 2, stable; and 3, less favorable).

stages were: Stage II (Mean, 115 U/L; elevated in 53%; normal in 30%), Stage III (Mean, 219; elevated in 23%; normal in 35%), and Stage IV (Mean, 302; elevated in 25%; normal in 35%) (Table 2). This data revealed that increasing ALP levels correlated with increasing stage (Mean, I = 115, III= 219, IV = 302; P = 0.0003). As apparent from this data, there is no difference at time of diagnosis, but there is clearly an increase in final ALP level as the stage increases.

Serum ALP levels were significantly elevated in 74% of patients with liver metastasis (Mean, 290 U/L) and in 33% without liver metastasis (Mean, 122 U/L) (P = 0.001) (Table 3). Patients with elevated ALP levels at the most recent time of progression were 5.7 (95% CI, 2.4-13.3) times more likely to have a liver metastasis compared to patients with normal levels. Additionally, patients with elevated ALP levels at their most recent visit were 4.2 (95% CI, 1.7-10.7) times more likely to have a worse prognosis compared to patients with normal levels. However, after controlling for the effects of liver metastasis, the association between elevated levels and prognosis was no longer significant.

After controlling for the effects of age, sex, and liver metastasis, large changes in ALP levels were associated with a 4.4 (95% CI, 1.0-19.1) times greater odds of having a worse prognosis compared to patients with a minimal change. Patients with an ALP level greater than 160 U/L were 12 (95% CI, 4.3-33.3) times more likely to have a liver metastasis than patients with an ALP level less than 160 U/L.

Mean carcinoembryonic antigen (CEA) levels (normal level for an individual is 3.0 ng/mL and 5.0 ng/mL in smokers) was 78 ng/mL for patients without liver metastasis and 308 ng/mL for patients with liver metastasis. CEA levels were compared against ALP in a random sample of 18 patients, which revealed a correlation between increasing levels of CEA (.002) with increasing levels of ALP.

DISCUSSION

Most data indicate that the elevation of serum ALP occurs because of the accelerated de novo synthesis of the enzyme and subsequent regurgitation into the serum.[1,2] An increased ALP is a common laboratory finding in colon cancer, especially with liver metastasis.[6] We found that serum ALP levels are significantly different among patients with and without a liver metastasis. This finding is

consistent among levels at the time of diagnosis as well as the final levels. Those with a liver metastasis have a significantly worse prognosis compared to those without. Patients with elevated final ALP levels have a 5.5 times greater odds of having a liver metastasis compared to those with normal ALP levels. This finding is significant as the 95% CI, 2.4-13.0. There is not a significant difference in age across stage; however, the mean age is lower among the stage IV patients. There is clearly an increase in final ALP level as stage increases. There is no difference at time of diagnosis, however. A greater percentage of females changed from normal to elevated ALP levels. There is a clear distinction of prognostic percentages between stages.

Osanaga et al[7] conducted a prospective, comparative study between alkaline phosphatase and gamma-glutamyltranspeptidase (GGT) in the diagnosis of hepatic metastases in 48 patients with digestive carcinomas. The ALP was less sensitive (0.50) than the GGT (0.86) but was more specific (0.96 as against 0.88). Diagnostic value of GGT (0.87) was therefore greater than of AP (0.75). Positive predictive value of AP was 0.70 and GGT was 0.57. The risk of detecting hepatic metastases was 9%, if the AP was normal and 2% if the GGT was normal. In another study, levels of GGT and total, alpha 2 and alpha 1-ALP versus dissemination pattern and survival time were studied in patients with stage III and IV tumors of various sites.[8] No significant changes in the activity of the said enzymes were registered in cases of single hepatic metastasis and metastasis-free liver. A slight increase in the enzymes' activity was observed in patients with pronounced liver involvement within months 10 to 4 before death. That was followed by a sharp and marked (3-4 times normal) rise in the levels during months 4 to 3. Changes in enzyme activity within the terminal 12 months were described with the aid of polynoms on the basis of regression analysis. A correlation between liver mass and degree of rise in serum enzymes levels was established. Viot et al[9] reported a new indicator, the isoenzyme of ALP migrating to the alpha 1 region (alpha 1 ALP), which appears to be more sensitive and more specific, capable of detecting 97% of liver metastases with a specificity of 90%, when compared to GGT and total ALP. Walach et al[10] compared peripheral blood leukocyte alkaline phosphatase (LAP) scores and plasma CEA levels in 26 patients with metastatic colorectal cancer to those in 30 healthy controls. Patients had metastases to the liver and abdomen. The mean LAP score in the metastatic CRC patients was significantly higher than in the control group (246 ± 65 vs 52 ± 26, $P < 0.001$); and the mean CEA level in the patients was also significantly higher than in the controls (110 ± 100 vs 4.9 ± 3 ng/mL, $P < 0.001$). One hundred percent of the metastatic CRC patients had elevated LAP scores and 73% of these patients had elevated CEA levels. There was a difference between the mean CEA levels in the patients with liver metastases and those with abdominal metastases (162 ± 135 vs 39 ± 53 ng/mL, $P < 0.04$). The results suggest that although both markers were elevated in metastatic CRC, the LAP score seems to be more useful in detecting metastatic disease, since we found 11% false negatives with the CEA level and 0% false negatives with the LAP score.

Our data and other studies do indicate that ALP, in addition to other markers can be used as a tool for biological detection of liver metastases.[11] The value of the serum activity of lactate dehydrogenase (LDH), ALP, and GGT have been compared with the findings from liver scintigraphy in 30 patients

with cancer.[12] Based on the results obtained, the authors concluded that the levels of biological markers were more significantly increased in malignant processes of the liver than scintigraphy of the liver could register. In 133 patients laparotomized for CRC the serum-5-nucleotidase, ALP and GGT were analysed preoperatively. The presence of liver metastases was established at laparotomy by palpation (prevalence 19%). The serum enzyme levels were elevated in 10% to 18% of patients without liver metastases and in 48% to 64% of patients with liver metastases. A comparison of the estimated tumor volume in the liver and the serum enzyme levels was performed. The predictive values of the three tests were computed at different reference limits. It was concluded that none of the tests used had any advantage over the other. To increase the diagnostic yield, another reference limit than normal at the laboratory, can be used. We conclude from our data that a change in ALP levels of greater than 120 U/L may be indicative of advanced disease progression. Prospective studies are indicated to confirm the role of ALP as a detective tool for liver metastasis as well as a prognostic factor in colorectal cancer. Monitoring the elevation of ALP levels in these patients may be economically used as an indicator of subsequent liver metastases, especially in the setting of surveillance after resection or adjuvant therapy. A retrospective review was undertaken to determine the influence of preoperative ALP levels on the prognosis of 26 patients who had undergone resection of liver metastasis from CRC at Roswell Park Cancer Institute.[6] Twenty of these patients were divided into two groups: group A consisted of 7 patients who survived at least 24 months without any evidence of disease and were free of disease at the time of this report. Group B consisted of 13 patients who recurred or died from metastases following liver resection. The preoperative levels of ALP clearly showed that an elevated level before surgery was associated with a poor prognosis in the majority of cases. In group A, only one of 7 patients had an elevated level where 7 of 13 patients in group B had elevated preoperative ALP levels. This small study suggested that preoperative alkaline phosphatase levels might be helpful in determining the prognosis of patients considered for curative resection of solitary liver metastasis from colorectal carcinoma. The decision to use certain chemotherapy agents in patients with CRC also seems to be related to ALP, as high bilirubin and ALP levels are associated with an exponential decrease in the clearance of irinotecan.[13]

CONCLUSION

Biological detection of liver metastases represents an important factor in the surveillance of the course of cancerous affections. Having a liver metastasis is the most important indicator of disease progression. This finding was evident even after controlling for the effects of age, sex, and other metastases. Monitoring the elevation of ALP levels at each patient's follow-up visit may be economically used as an indicator of subsequent liver metastases. Furthermore, a change in ALP levels of greater than 120 U/L over a period of 4 to 6 months may be indicative of advanced disease progression, which warrants a more aggressive treatment or a change in regimen. ALP is a simple, low cost, relatively sensitive screening tool for detecting liver metastases. Future studies aiming at better defining the role of ALP in colon cancer is prudent.

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