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Research Article

Prognostic Significance of Hemoglobin, Albumin, Sedimentation, CRP, CEA, CA19-9 and Lipid Profile at the Time of Diagnosis in Patients with Metastatic Gastrointestinal System Cancers and Association with Response to Systemic Chemotherapy

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Abstract

Objectives: Gastrointestinal cancers are common and lethal. Therefore new prognostic parameters are needed. In this study,we investigated the relationship between hemoglobin,sedimentation, crp, albumin, CEA, CA19-9 and serum lipid profile with prognosis and response to treatment in patients with metastatic gastrointestinal system cancer.

Methods: Between April 2010 and September 2012, patients with gastrointestinal system cancers, who had been followed up in the Department of Medical Oncology, Ankara University Faculty of Medicine, were analyzed retrospectively. We evaluated 25 patients for research group and 25 patients with non-metastatic gastrointestinal system cancers for control group. First, the groups were compared between themselves according to their baseline values. Then,pre-chemotherapy and post-chemotherapy blood values were compared in the metastatic group.

Results: There was no significant difference between the groups in terms of age and gender (p>0.05). There was no statistically significant differences between the research and control groups except for baseline CEA levels. Basal CEA levels in research patients were significantly higher (p=0.006). After chemotherapy, objective response was achieved in 20 %of metastatic patients; while the disease was stable or progressive in 80% of patients. After chemotherapy, CRP levels decreased, HDL-C increased and TC/HDL-C ratio decreased in the all chemotherapy responder patients(n=5) compared to the baseline values.

Conclusion: This study showed for the first time that HDL-C increased and the TC/HDL-C ratio decreased in patients with metastatic CRC who responded to chemotherapy. These changes in lipid parameters were correlated with CEA changes.

Keywords: Chemotherapy Respons, Gastrointestinal Cancers, Prognostic Factors

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Gastrointestinal cancers are one of the primary causes of cancer-associated deaths. due to their high frequency and lethality, new prognostic indicators are needed to determine their relationship with the prognosis of the disease and response to treatment. In this study, it was aimed to investigate the prognosis of the disease and its relationship with the response to treatment by analyzing the hemoglobin (Hb), serum albumin, erythrocyte sedimentation rate (ESH), C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) and serum lipid profile at the time of diagnosis and during follow-up in "patients with metastatic gastrointestinal system cancer".

Methods

For this study, a search was conducted in the hospital's computer archive registry system, and the patients diagnosed with gastrointestinal system cancer who were followed up and treated between April 2010 and September 2012 in Ankara University Faculty of Medicine, Department of Internal Medicine, Field of Medical Oncology, outpatient clinic and service were selected. Patients who underwent erythrocyte suspension and albumin replacement, received antihyperlipidemic therapy, and had signs of infection at diagnosis were not included in the study.

A total of 50 patients were studied in this study. Since it was determined that 25 patients could be included in the study group, 25 patients with gastrointestinal system cancer without metastasis were selected as the control group. The male/female ratio in the study group with metastasis was 17/8, and the male/female ratio in the control group was 13/12 (Table 1). Efforts were made to ensure that the patients selected for the control group were similar to the "research group patients" in terms of primary malignancy. The patients were divided into 2 groups as "with metastasis" and "without metastasis". The groups were first compared among themselves according to their baseline values. Then, pre-chemotherapy and post-chemotherapy blood values were compared in the metastatic group. In metastatic patients, hemoglobin, albumin, erythrocyte sedimentation rate (ESH), C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and fasting serum lipid profile values were checked at the time of diagnosis and after at least 2 cycles of chemotherapy. Since these tests were requested from the patients during their routine examinations, a separate budget was not required to be created. At the controls of metastatic patients 2-3 months later, re-ordering of hemoglobin, albumin, ESR, CRP, CEA, CA19-9 and fasting serum lipid profile tests were recorded in their files.

Table 1. Age-sex and cancer distributions between groups

	Group with metastasis (n=25)	Group without metastasis (n=25)
Age (Year)	58.84±11.65	61±8.73
Male/Female	17/8	13/12
Esophagus	2	0
Stomach	7	9
Colorectal	10	12
Pancreas	5	3
Cholangiocellular	1	1

Statistical Analysis

The comparison of metastatic and non-metastatic groups in terms of age and baseline values was performed with the 'Student's t-test' or 'Mann Whitney U' test for independent groups, depending on whether or not the data showed normal distribution. Baseline and post-chemotherapy evaluation of the metastatic group was performed with Student's t test or Wilcoxon test in dependent groups. Chi-square and 'Fisher's Exact chi-square' tests were used to compare gender and PS values between metastatic and non-metastatic groups, respectively. The data obtained from the measurement were summarized as mean±standard deviation or median (minimum-maximum), and categorical data were summarized as frequency and percentage. All analyzes were performed with the SPSS 15.0 for Windows package program. $P<0.05$ was considered statistically significant.

Results

A total of 55 patients, 30 with and 25 without metastasis, were included in the study. 4 of the patients in the group with metastasis with PS:2-3 at diagnosis (diagnosed with 2 colon, 1 pancreatic, 1 esophageal cancer) died after 1 cure of chemotherapy. One patient with a diagnosis of metastatic gastric cancer continued their follow-up and treatment in their center after receiving their first chemotherapy. The "research group" was formed with 25 patients with metastases who could be followed up. As a result, the study was completed with 25 patients with metastases and 25 patients without metastases (control group).

Two-thirds of the research (with metastases) group were male. In the control group, on the other hand, although the male/female ratio was close to one, there was no statistical difference between the two groups in terms of gender distribution. The mean age was 61±8.73 years in the study group and 58.8±11.6 years in the control group. There was no significant difference between the groups in terms of age ($p>0.05$). The age-gender distributions of the patient and control groups are given in Table 1. Colon cancer was the majority in both groups. The most common were liver

metastases. Other sites of metastases included the lung, peritoneum, bone, and brain.

No significant difference was detected between the groups in terms of hemoglobin, serum albumin, ESR and CRP levels. Baseline CEA levels were found to be statistically higher in the patient group with metastasis (p=0.006). Although the CA19-9 level was not statistically significant, it was found to be higher in the group with metastasis (p=0.641). The "baseline values" of the patients in both groups are given in Tables 2 and 3. The values given in Table 2 were calculated with the non-parametric test, and the values given in Table 3 were calculated with the parametric test.

No statistically significant difference was found between the groups with and without metastasis in terms of baseline HDL-C and TC/HDL-C measured before chemotherapy (p=0.69 and p=0.869). Likewise, the difference between the groups in terms of TC, LDL-C and TG was not statistically significant (p=0.867, p=0.977, p=0.24, respectively).

After chemotherapy, 20% of the patients in the study group had an objective response, and 80% had stable or progressive disease. Of the 5 patients who received chemotherapy response, 4 had colorectal cancer and one had cholangiocellular cancer.

One patient who underwent erythrocyte suspension and albumin replacement after the first course of chemotherapy was not included in the response assessment in terms of hemoglobin and albumin. Likewise, 5 patients were not included in the post-chemotherapy response evaluation in terms of ESR and CRP due to various foci of infection (surgical suture infection, intra-abdominal abscess, pneumonia, UTI).

No significant difference was found in the hemoglobin, albumin and ESR values examined before and after chemotherapy (Table 4).

It was found that patients with objective chemotherapy response (n=5) had lower baseline CRP levels (p=0.297), although not statistically significant, and that the baseline CEA (p=0.06) and CA 19-9 (p=0.668) levels were higher than the patients with no chemotherapy response (n=20) (Table 5).

No statistically significant difference was found between the baseline T. Cholesterol, HDL, LDL, VLDL, TG, and TC/HDL-C ratios of patients (n=5) and patients without objective chemotherapy response (n=20) (Table 6).

It was found that the CRP values of patients with an objective chemotherapy response (n=5) were lower than their baseline values (from 3.0 to 1). It was observed that the CRP levels of the patients with no chemotherapy response

Table 2. Comparison of baseline parameters in groups with and without metastasis-1

	Group with metastasis			Group without metastasis			P
	Median	Minimum	Maximum	Median	Minimum	Maximum	
VLDL (mg/dL)	27	7	64	23	6	76	0.232
TG (mg/dL)	136	35	322	115	31	381	0.240
ESH (mm/saat)	18	2	84	26	12	77	0.052
Baseline CRP (mg/L)	3.65	0.1	59.4	4.64	0.8	111	0.379
Baseline CEA (ng/mL)	11.67	0.9	999	2.07	0.47	23.4	0.006
Baseline CA 19-9 (U/mL)	25.2	0.8	1917.8	11.8	1	306.2	0.641
Baseline TC/ HDL-K	5.12	2.63	19.54	4.83	2.7	7.9	0.869

VLDL: Very Low Density Lipoprotein; TG: Triglyceride; ESH: erythrocyte sedimentation rate; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; TC: Total Cholesterol; HDL: High Density Lipoprotein.

Table 3. Comparison of baseline parameters in groups with and without metastasis-2

	With metastasis	Without metastasis	P
Baseline Hb (g/dL)	11.96±1.94	12.00±1.98	0.931
Baseline Albumin (g/dL)	3.44±0.60	3.52±0.46	0.620
Baseline T. Cholesterol (mg/dL)	174.28±50.17	171.96±46.90	0.867
Baseline LDL (mg/dL)	111.17±40.77	111.50±39.72	0.977
Baseline HDL (mg/dL)	34.08±11.62	35.3±9.74	0.690

Hb: Hemoglobin; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein.

Table 4. Comparison of parameters before and after chemotherapy in the group with metastasis

	Pre-Chemotherapy	Post-Chemotherapy	P
Hb (g/dL)	12.08±1.88	11.77±1.17	0.451
Albumin (g/dL)	3.44±0.6	3.41±0.58	0.822
ESH (mm/hour)	28.1±25.2	25.7±20	0.632

Hb: Hemoglobin; ESH: Erythrocyte Sedimentation Rate.

did not change much (from baseline 4.32 to 4.1). CRP levels after chemotherapy were found to be significantly different in groups with and without chemotherapy response (p=0.019). Likewise, CEA and CA 19-9 levels decreased after chemotherapy in patients with chemotherapy response, while these values increased in patients without chemotherapy response (Table 7).

No statistically significant difference was found between T.Cholesterol, HDL, LDL and TC/HDL-C after chemotherapy between patients with (n=5) and without (n=20) objective chemotherapy response. However, TG and VLDL levels were found to be statistically higher in patients with CT response (p= 0.029, p= 0.024, respectively). It was observed that HDL levels increased and TC/HDL-C ratio decreased after chemotherapy in both groups (Table 8).

It was found that the ratio of TC/HDL decreased in all 5 patients who received FOLFOX treatment and 3 patients who received XELOX treatment. While 3 of 5 patients who received FOLFOX responded to chemotherapy, stable disease was detected in 2 patients. Stable disease developed in 2 of 3 patients who received XELOX, and progressive disease in 1 patient. The change in the TC/HDL ratio of the patients according to the CT protocols is given in Table 9.

Table 5. Comparison of baseline parameters of patients with metastases with and without chemotherapy response-1

	With chemotherapy response (n=5)			Without chemotherapy response (n=20)			
	Median	Minimum	Maximum	Median	Minimum	Maximum	P
CRP (mg/L)	3	0.8	5.1	4.32	0.1	59.4	0.297
CEA (ng/dL)	72.4	3.49	192.1	5.34	0.9	999	0.06
CA 19-9 (U/dL)	124	0.8	912.2	25.15	0.8	1917.8	0.668

CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9.

Table 6. Comparison of baseline parameters of patients with metastases, with and without chemotherapy response-2

	With chemotherapy response (n=5)	Without chemotherapy response (n=20)	p
T. Cholesterol (mg/dL)	219±17.5	163.1±49.5	0.12
HDL (mg/dL)	39.3±14.6	32.7±10.7	0.408
LDL (mg/dL)	143±14	103.2±41.5	0.51
VLDL (mg/dL)	36.8±18.4	27.1±14.3	0.371
TG (mg/dL)	184±92	135.4±72.1	0.371
TC/HDL-K (mg/dL)	6.4±2.9	5.6±3.5	0.717

TC: Total Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; TG: Triglyceride.

Table 7. Comparison of post-chemotherapy parameters of patients with metastases with and without chemotherapy response-1

	With chemotherapy response (n=5)			Without chemotherapy response (n=20)			P
	Median	Minimum	Maximum	Median	Minimum	Maximum	
CRP (mg/L)	1.1	0.8	2.8	4.1	1	212.9	0.019
CEA (ng/dL)	3.48	1.4	11.39	5.24	0.49	433	0.53
CA 19-9 (U/dL)	18.8	0.8	39.4	36.45	0.8	1983	0.112

CRP: C-reactive protein, CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9.

Table 8. Comparison of post-chemotherapy parameters of patients with metastases with and without chemotherapy response-2

	With chemotherapy response (n=5)	Without chemotherapy response (n=20)	p
T.Cholesterol (mg/dL)	210.4±12.6	178.7±43.1	0.83
HDL (mg/dL)	44.4±15	44.8±17.5	1.00
LDL (mg/dL)	127.1±21.6	108.9±38.3	0.243
VLDL (mg/dL)	39±13.1	24.9±13.2	0.024
TG (mg/dL)	194.2±65.9	122.7±67.9	0.029
TC/HDL-K (mg/dL)	5.2±1.7	4.3±1.6	0.243

TC: Total Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; TG: Triglyceride.

Table 9. Change of TC/HDL ratio according to chemotherapy protocols

	Those whose TC/HDK ratio has decreased	Those whose TC/HDK ratio has increased	Total
Cisplatin+5FU	1	1	2
Cisplatin+Gemcitabine	2	2	4
DCF	3	3	6
FOLFOX	5	0	5
FOLFIRI	1	0	1
FUFA	0	1	1
Gemcitabine	0	1	1
Carboplatin+Gemcitabine	1	0	1
XELODA	0	1	1
XELOX	3	0	3
TOTAL	16	9	25

DCF: Docetaxei, Cisplatin, 5-Fluorouracil; FOLFOX: Folinic acid, 5- Fluorouracil, Oxaliplatin; FOLFIRI: Folinic acid, 5- Fluorouracil, Irinotecan FUFA: Folinic acid, 5- Fluorouracil, XELODA: Capecitabine XELOX: Capecitabine, Oxaliplatin.

Discussion

The number of predictive factors for pre-detection of patients who may benefit from chemotherapy is small. In predicting chemotherapy response in these patients, the 'performance status' of patients is generally accepted as a good indicator and palliative chemotherapy is not recommended for patients with performance status 3-4. However, various studies have been carried out to determine which patient can respond well to chemotherapy and to determine a parameter that can be used clinically in determining the prognosis.[1,2]

In our study, it was found that the median baseline CEA values of the patients with metastases were statistically higher than the preoperative baseline CEA levels of the patients without metastasis (p=0.006). No other similar study could be found on why patients with metastases with higher serum CEA levels 'respond better to chemotherapy' than those with lower CEA levels. It was observed that CEA and CA 19-9 levels decreased after chemotherapy in all 5 patients with objective chemotherapy response in the group with metastasis, while these tumor markers increased after chemotherapy in the group without chemotherapy response, compared to baseline.

In a retrospective study that Boonpipattanapong T et al. conducted in patients with colorectal carcinoma, the relationship between preoperative CEA and albumin levels and survival was investigated, and a statistically significant difference was found between well-differentiated, low-CEA-level tumors and poorly-differentiated, high-CEA-level tumors (p=0115). It has been reported that preoperative CEA ≥5 ng/mL and albumin ≤3.5 g/dL adversely affect survival in patients with colorectal carcinoma.[3] However, in our study, the difference was not statistically significant in terms of baseline albumin values (p=0.620).

Some hypotheses have been proposed by investigating various mechanisms between cancer development and serum lipid level. It is known that lipid peroxides formed as a result of peroxidation of lipoproteins by free radicals cause cellular damage and inflammatory response. Accordingly, they cause malignant transformation in normal cells.

[4] It has been suggested that the decrease in HDL level as well as the increase in LDL level lead to an increase in proinflammatory activity such as TNF-alpha and IL-6.[5] There are many studies showing that statins, which are widely used and act by inhibiting HMG-CoA reductase, reduce the risk of colorectal and gastric cancer.[6,7] In their study, Wulaningsih et al. found a positive correlation ($p<0.001$) between high TG, low HDL and esophageal cancer, and a negative correlation with other lipid parameters (LDL, LDL/HDL, TC/HDL, ApoB/ApoA). It was found that the risk of gastric cancer increased in those with low HDL levels, although not statistically significant. It was found that the risk of gastric cancer increased in those with low HDL levels, although not statistically significant.

No statistically significant difference was found in our study in terms of baseline HDL-C and TC/HDL-C measured before chemotherapy ($p=0.69$ and $p=0.869$). Likewise, the difference between the groups in terms of TC, LDL-C and TG was not statistically significant ($p=0.867$, $p=0.977$, $p=0.24$, respectively). In the metastatic group, TC/HDL and TG levels were found to be higher, although not statistically significant. It was thought that this might show that there is no relationship between the lipid profiles of patients with gastrointestinal cancer and their tumor burden, or that it may be due to the insufficient number of patients in the study.

No statistically significant difference was found between baseline T. Cholesterol, HDL, LDL, VLDL, TG and TC/HDL-C ratios of patients with (n=5) and without (n=20) objective chemotherapy response. However, although TG and VLDL levels were found to be statistically higher in patients with CT response after chemotherapy, it does not seem possible to make a further interpretation due to the small number of patients. It was found that HDL levels increased and T.Cholesterol/HDL ratio decreased after chemotherapy in all 5 patients with objective chemotherapy response. This change was found to be correlated with the decrease in CEA level. It has been stated in previous studies that high HDL, low TC/HDL-K ratio prevents peroxidation in lipoproteins and prevents cellular damage caused by lipid peroxides, thus preventing malignant transformation in normal cells. However, in our study, it was found that the HDL level increased after chemotherapy and the TC/HDL-C ratio decreased in the group without objective chemotherapy response. The relationship of this condition with prognosis could not be demonstrated in our study.

It was found in our study that HDL Cholesterol increased and TC/HDL-C ratio decreased in chemotherapy regimens in which oxaliplatin and fluorouracil infusion were applied due to metastatic colon cancer. This situation suggested that the regimens where oxaliplatin and fluorouracil are used together may have an effect on increasing HDL and decreasing the TC/HDL-C ratio. However, 3 of 5 patients who were administered FOLFOX responded to chemotherapy, while 2 patients had stable disease. No previous studies were found in the literature on the effects of these chemotherapeutics on the lipid profile. Due to the insufficient number of patients, no comment could be made on this issue. It was thought that studies with more patients were needed to prove this effect.

In this study, besides the lipid profile, the relationship between CRP and prognosis in patients with gastrointestinal cancer was also examined. Many studies have been conducted showing that the risk of colorectal cancer increases in ulcerative colitis and Crohn's disease, which are known as inflammatory bowel diseases, and this risk decreases in those receiving long-term anti-inflammatory treatment (ASA and other NSAI drugs), and therefore inflammation may play a role in the development of colorectal cancer.[9, 10] Also, many studies have reported that preoperative serum CRP levels are correlated with the stage of cancer in patients with colorectal cancer. CRP levels were found to be much higher in advanced stage patients.[11,12] In our study, on the other hand, the median CRP was found to be 3.65 mg/L in the group with metastasis and a median CRP of 4.64 in the group without metastasis. Our study was compatible with the study conducted by Yüceyar S. et al. However, there are also hypotheses in the literature that the level of CRP increases after the onset of colorectal cancer, especially in the first 2 years.[13,14] Therefore, the inflammatory response of the immune system will also increase, with the increase in the tumor burden. Therefore, in the metastatic group, the CRP level may increase more in the follow-up. As a matter of fact, it was found in our study that the CRP levels of patients with objective chemotherapy response (n=5) were significantly lower than those without chemotherapy response (n=20). Additionally, it was found that CRP levels decreased compared to baseline after chemotherapy in all patients with chemotherapy response, while CRP levels were found to increase compared to baseline in those with no chemotherapy response. We believe that CRP levels reflecting inflammation will also decrease in patients whose tumor burden is reduced by chemotherapy, and that this may be used as a new marker in the evaluation of response to chemotherapy and disease prognosis.

In conclusion, no significant difference was found in our study between the groups with and without metastasis in baseline parameters, except for the CEA level. However, it was observed that patients with higher baseline CEA levels responded better to chemotherapy. It was found that HDL-C increased and TC/HDL-C ratio decreased after chemotherapy in all patients with chemotherapy response. In this

study, it was shown for the first time that HDL-C increased and TC/HDL-C ratio decreased in responding patients in the evaluation of chemotherapy response in metastatic patients with colorectal cancer. These changes in lipid parameters were correlated with CEA changes. It was concluded that it would be appropriate to continue this study in patients with colorectal cancer.

Disclosures

Ethics Committee Approval: Ethics committee approval was not recevied for this retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.A., A.D.; Design – A.A., A.D.; Supervision – A.D.; Materials – A.A., A.D.; Data colection and processing – A.A.; Analysis and/or interpretation – A.A., A.D.; Literature search – A.A., A.D., Writing – A.A.; Critical review – A.D.

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