Following Chemotherapy: Serum Cytokine (Tumor Necrosis Factor, Interleukin-2, Interleukin-11), Immunoglobulin, Complement, Vascular Endothelial Growth Factor Levels, and the Systemic Symptoms like Capillary Leak Syndrome

Biomarkers in Cancer
Volume 11: 1–9

DOI: 10.1177/1179299X19854447
SAGE

Havva Keskin[1], Kenan Cadirci[2], Ahmet Demirkazik[3], Hakan Akbulut[3] and Bulent Yalcin[4]

[1]Department of Internal Medicine, Istanbul Medeniyet University Training and Research Hospital, Istanbul, Turkey. [2]Department of Internal Medicine, Erzurum Regional Training and Research Hospital, Erzurum, Turkey. [3]Department of Medical Oncology, Faculty of Medicine, University of Ankara, Ankara, Turkey. [4]Department of Medical Oncology, Faculty of Medicine, University of Yildirim Beyazit and Atatürk Training and Research Hospital, Ankara, Turkey.

ABSTRACT: Several problems such as myalgia, arthralgia, fever, dyspnea, generalized edema, and pleural effusion can occur in cancer patients following the chemotherapy, especially at the first cycle of the first chemotherapy treatment. Although it is assumed that some cytokines are associated with the development of these symptoms and signs, their pathophysiology has not been discovered completely yet. They are usually mild, but they may rarely progress to the severe stage of "Systemic Capillary Leak Syndrome" with a high mortality rate. The objective of this study was to investigate the association between the serum levels of interleukin-2 (IL-2), interleukin-11 (IL-11), tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF), and these symptoms and signs. A total of 44 cancer patients who had neither heart, lung, liver, renal, or thyroid disease were recruited into this study. Their symptoms and signs were examined and questioned before the first cycle of the first chemotherapy treatment and the 24 h after this chemotherapy. All participant's serum samples were taken, and the VEGF, TNF, IL-2, and IL-11 levels were studied. There was no association between the chemotherapeutic drugs, and the symptoms and signs such as edema, dyspnea, coughing, and flu-like symptoms. There was a significant decrease in IL-11 levels in the other treatment group compared with the group receiving paclitaxel, docetaxel, gemcitabine, and vinorelbine in the first day following chemotherapy ($P = .006$). However, no relation was observed between the symptoms and signs, the response to the chemotherapy, and the serum levels of VEGF, TNF, IL-2, and IL-11. These symptoms and life-threatening syndrome have been a current topic between the clinicians. Although some drugs and mediators are accused, its pathophysiology has not been discovered completely yet. In this study, we could not detect any association between the symptoms, signs, and the cytokine levels following the chemotherapy.

KEYWORDS: Chemotherapy, serum cytokines, vascular endothelial growth factor, systemic symptoms, capillary leak syndrome

RECEIVED: May 1, 2019. **ACCEPTED:** May 8, 2019.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Havva Keskin, Department of Internal Medicine, Istanbul Medeniyet University Training and Research Hospital, 34772 Istanbul, Turkey.
Email: havva.drkeskin@gmail.com

Introduction

Several problems such as myalgia, arthralgia, fever, dyspnea, generalized edema, and pleural effusion can occur in cancer patients. These symptoms and signs may appear more frequently following up the chemotherapy treatment especially the first cycle of the first chemotherapy treatment. The pathophysiology of these symptoms and signs has not been discovered entirely yet. They are usually mild, but they may rarely progress to the severe stage that is known as "Systemic Capillary Leak Syndrome."[1-3]

Systemic capillary leak syndrome can be characterized by recurrent, reversible episodes of shock and peripheral edema with high mortality. It is seen equally in both genders. This life-threatening syndrome is a sudden and unexplained leakage of plasma into the tissues. The syndrome can follow the chemotherapy treatment, especially the first cycle of first chemotherapy treatment. However, the syndrome cannot occur only in the following first cycle of the first chemotherapy treatment, but can also occur in the different periods of different chemotherapy treatment protocols and in patients with sepsis, angioedema, snake bite, and systemic anaphylaxis.[4-6]

As it is known, this syndrome is not unique to the patients who take a chemotherapy treatment. They can appear in patients who have heart disease, lung disease, kidney disease, and hypothyroidism.[5,6] If a chemotherapy treatment contains paclitaxel, docetaxel, gemcitabine, or vinorelbine, these symptoms and signs can occur more often than the chemotherapy treatment not containing these drugs, but the pathophysiology is still not clear.[5-8] While the mechanism is unclear, it is thought that these drugs stimulate the synthesis and release of some cytokines. This altering of the balance of the cytokines causes changes in the balance of acute phase proteins, complement, and immunoglobulins in serum.[4-6,9,10] Also, similar side effects can occur during the usage of these cytokines for different indications.[11] Therefore, it is thought that these cytokines can play a key role in the pathophysiology of this

syndrome and these symptoms and signs.[4-6] When deciding on the cytokines to be studied, previous literature has been analyzed and it has been decided to study interleukin (IL)-2, IL-11, tumor necrosis factor alpha (TNF-α), and vascular endothelial growth factor (VEGF). These molecules have been previously accused that they cause similar side effects to symptoms and signs mentioned before during immunotherapy usage.[1,4-6,12,13]

Although these symptoms and signs (generalized edema, hypotension, shortness of breath, fatigue, widespread muscle and joint pain, numbness, and skin rash) are not as severe as those in the systemic capillary leak syndrome, the clinical symptoms and signs are similar to each other. From this point, we hypothesized that the pathophysiology of the symptoms and signs are similar to the pathophysiology of the systemic capillary leak syndrome. In this study, the relation between these symptoms and signs and the serum levels of the cytokine such as IL-2, IL-11, TNF-α, and VEGF was investigated. It was also investigated the changes of the cytokine level and the response to the chemotherapy treatment.

Patients and Methods

A total of 44 cancer patients (26 males and 18 females) who had a tissue diagnosis were recruited into this study. All of these cases did not previously receive any treatment (chemotherapy/radiotherapy) for cancer disease. All of them were chosen from Ankara University Hospital, Department of Medical Oncology Clinic. Some cases were selected from hospitalized patients and the other ones were selected from ambulatory cases who were resident in Ankara city. Cases who had heart, lung, liver or kidney disease, ongoing infection, any chronic inflammatory disease, autoimmune disease, and used of steroid or any other drug that is affecting on immunoreaction were excluded from the study.

The previous clinical studies and the clinical experiences have shown that these symptoms and signs can be seen after the second and third chemotherapy but they occur more common followed by the first chemotherapy.[14] For this reason, in our study, considering the cost and the difficulty of following-up due to the prospective design, it was considered more appropriate to examine only the first cycle of the first chemotherapy treatment where these symptoms and signs were most frequently observed according to the results of these previous studies. In addition, considering the cost again, IL-2, IL-11, TNF-α, and VEGF levels were measured only in the first-day serum samples. Since the blood half-life of the cytokines is short, the blood samples were obtained in 24 h follow of the chemotherapy. These blood samples were delivered to the nearest laboratory in 20 min. Then, the serum samples were separated by centrifugation at 5000 r/min for 5 min. These serum samples were placed in Eppendorf tube and stored at − °75 C. Hemoglobin, hematocrit, sedimentation, blood urea nitrogen, creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), complement C3 and C4, immunoglobulins IgG, IgA, IgM, protein electrophoresis, spot urine protein, spot urine density, urine osmolarity, and serum osmolarity also measured before the chemotherapy treatment and on the first day after this treatment. Free-T3, free-T4, and TSH were also measured before the treatment. All of these parameters were analyzed at Ankara University Medical Faculty Hospital Laboratories. Besides the blood samples were obtained from all participants, a questionnaire and a physical examination were also simultaneously applied to all participants to observe whether there are lower extremity edema, weakness, shortness of breath, fever, rash-itch on the skin, voice misery, cough, muscle, and joint pain.

All serum samples were removed from −75°C, and they were put in dry ice to be transported to the laboratory where the cytokines were studied. Then, all samples were allowed to stand at room temperature for melting before being analyzed. The samples were run in duplicate, and the results were evaluated as picogram/milliliter. The measurements of VEGF, TNF, IL-2, and IL-11 were made using the enzyme-linked immunosorbent assay (ELISA) method on the device named "Medispec ESR-200 Microplate Reader" which belongs to "IBM."

Statistical analysis

Kolmogorov-Smirnov normality test was used to analyze the normality of the distribution. Then, the paired sample *t* test was used for the normal distributions while the Wilcoxon test was used for the non-normal distributions. If one of the two dependent variables showed a normal distribution, the paired sample *t* test was used in the analysis. The results were reported with 95% confidence interval. The *P*-value of $<.05$ was considered significant. All statistical analyses in this study were performed using SPSS 20.0 software program (SPSS Inc., Chicago, IL). Written informed consent was obtained from all participants, and the study was approved by the ethical committee of Erzurum Training and Research Hospital, Turkey (2818/16-154).

Results

Serum cytokine levels, survey records, and physical examinations records were analyzed in 44 patients (26 males, 18 females; mean age: 52 ± 12 years, and age range: 26-73 years). The study participants were heterogeneous for the diagnoses, treatment protocols, and age ranges. Patients with lung cancer (27 cases with 8 small cells, 19 non-small cells; mean age: 57.7 ± 9.7 years, and age range: 35-73 years) were in the majority of the study participants. The other cases (3 males, 14 females; mean age: 47.2 ± 11.2 years, and age range: 26-63 years) were consisted of 11 operated breast cancer, 2 operated gastric carcinoma, 1 operated colon carcinoma, 1 operated ovarian cancer, 1 metastatic gastric carcinoma patient who had neoadjuvant chemotherapy, 1 local advanced gastric, and 1 pancreatic carcinoma. All the operated patients were under adjuvant chemotherapy medication. The demographic and

clinical characteristics of the patients can be seen in Table 1. There was no tumor tissue in the lungs of any patient except lung cancer cases (no lung metastasis in any patient).

There were not enough cases to separate into the 5 groups as the patient who takes paclitaxel, docetaxel, gemcitabine, or vinorelbine and the other agents because the diagnoses and the treatment protocols of the patients were quite heterogeneous. Therefore, all the participants were divided into two groups. One of the groups (paclitaxel, docetaxel, gemcitabine, or vinorelbine [PDGV]) included patients who had paclitaxel, docetaxel, gemcitabine, or vinorelbine therapy, which we expect most symptoms and signs would be developed in. The other group of patients were received the chemotherapy drugs other than paclitaxel, docetaxel, gemcitabine, vinorelbine. According to the treatment protocols, there were 21 patients in PDGV treatment group and 23 patients in the other treatment group. More detailed information about the treatment procedures can be seen in more detail in Table 1.

There was no difference in both treatment groups for the sedimentation, serum protein electrophoresis, complement, and immunoglobulin levels. The decreasing of hematocrit was significant in the other treatment group ($P = .013$) while the hemoglobin levels were not changing ($P = .157$) in the same group (Table 2). When the symptoms and signs were compared from the baseline to the first-day, regardless of the treatment protocols, there were significant differences between the baseline and the first-day values of the body weight. The increase of the leg circumferences was significant in the other treatment group than the PDGV group. When it was evaluated according to the treatment protocols, the systolic blood pressure was increased ($P = .025$) after taking the PDGV treatment while the diastolic blood pressure was not changed ($P = .331$) in the same group (Table 3). According to the PDGV group which was formed with the patients who had the paclitaxel, docetaxel, gemcitabine, and vinorelbine therapy, there was a more significant decrease in serum IL-11 levels after the chemotherapy treatment in the other treatment group ($P = .006$) (Table 4). However, there was no significant difference in the VEGF, TNF, and IL-2 levels in the whole study group and the two treatment subgroups (Table 4).

There was no statistical difference in both treatment groups for the weakness, shortness of breath, fever, rash-itch on the skin, voice misery, cough, muscle, and joint pain. However, the skin rash and the hoarseness were appeared in 2 patients in the PDGV group, and in 1 patient in the other treatment group. The shortness of breath was detected in 1 patient in PDGV group and in 4 patients in the other treatment group. Also, after 10-12 hours the chemotherapy, 3 patients who received vinorelbine reported shortness of breath which it took half an hour and spontaneously recovered. It was detected cough in 2 patients who one of them received vinorelbine and the other one received gemcitabine in the PDGV group. The cough was also detected in 4 patients in the other treatment group. When assessed the muscle and joint pain, these symptoms were observed in 2 patients. One of them was in the vinorelbine therapy subgroup of the PDGV group, and the other one was in the other treatment group. They can be seen in Table 3.

It was not found any relation between the cytokine level changes and the chemotherapy response. Also, it was not seen any association between the developing signs and symptoms and the response of the chemotherapy.

Discussion

In the present study, it was investigated the relationship between the serum cytokine levels (VEGF, TNF-α, IL-2, and IL-11) and some symptoms and signs before and after the chemotherapy treatment. It was also investigated whether there is a relationship between the changing of the cytokine levels, symptoms, and signs and the chemotherapy response in these cases. Previous chemotherapy experiences have been shown that patients who were treated with paclitaxel, docetaxel, gemcitabine, or vinorelbine had the symptoms and signs such as a cough, flu-like symptoms, edema, and pain more frequently than the patients who were treated with other chemotherapeutic agents.[15-18] Based on our clinical observation and the previous chemotherapy experiences, in this study, patients who took the paclitaxel, docetaxel, gemcitabine, or vinorelbine were grouped into one group (PDGV group), and the other chemotherapy protocols were evaluated as "the other group." However, no patients with clinical symptoms and signs of capillary escape syndrome were found in neither group. Since it is known that this syndrome is rarely observed, the symptoms and signs suspected of being similar to the pathophysiology were questioned, but there was also no difference between the groups in terms of symptoms and signs.[15,17,19]

Amoura et al[16], and Kawabe et al[20] evaluated 69 patients with systemic capillary leak syndrome, retrospectively. They detected an elevation of hemoglobin, hematocrit, blood urea nitrogen, creatinine, and monoclonal IgG levels while a decreased of serum total protein and albumin levels without proteinuria, and also the changes in serum complement C3 and C4 levels (increased in some cases, decreased in some other cases).[11,16,20] In addition, Amoura et al[16] reported that 4 out of 13 patients had upper respiratory tract infection history in 2 weeks before receiving the chemotherapy treatment.[16] In our study, it was not questioned whether the participants had any infection before the treatment period. We asked whether there was any infection at that moment. If there was an infection at that moment, the patient was not enrolled in the study. We detected also decrease in hematocrit, especially in the other treatment group. The fell in hematocrit could be based on the serum dilution due to the water retention. Increased the body weight and the leg circumferences were also supporting the water retention hypothesis. It was not found a significant change in other parameters in our study.

The relationship between IL-11 and the prognosis of patients with various cancers have been investigated in several studies. One of them was carried out by Berry et al.[21] They

Table 1. Demographic, clinical characteristics and the treatment protocols for all cases.

CHARACTERISTICS OF PATIENTS	NUMBER OF PATIENTS (N=44)	%
Age (min-max)	52 (26-73)	
Gender		
Male	26	59.1
Female	18	40.9
Primary tumor locations		
Lung	27	61.4
Breast[a]	11	25.0
Over[a]	1	2.3
Colon[a]	1	2.3
Pancreas	1	2.3
Stomach		
Adjuvant	2	4.5
Neoadjuvant	1	2.3
Chemotherapeutic agents administered		
PDGV group (total)[b]	21	47.7
Cisplatin + vinorelbine	7	15.9
Cisplatin + gemcitabine	3	6.9
Cisplatin + docetaxel	2	4.5
Cisplatin + paclitaxel	2	4.5
Carboplatin + paclitaxel	6	13.6
Paclitaxel	1	2.3
Other chemotherapy group (total)[c]	23	52.3
Cyclophosphamide + adriamycin (adjuvant)	5	11.3
Cyclophosphamide + adriamycin	4	9.1
Cyclophosphamide + adriamycin + 5-fluorouracil	2	4.6
Cisplatin + etoposide	8	18.1
Cisplatin + epirubicin	1	2.3
Cisplatin + 5-fluorouracil	1	2.3
Irinotecan + 5-fluorouracil	1	2.3
5-Fluorouracil (adjuvant)	1	2.3

Abbreviation: PDGV, paclitaxel, docetaxel, gemcitabine, or vinorelbine.
[a]Patients in complete remission following surgery who have undergone adjuvant chemotherapy.
[b]Patients who have been administered any of the paclitaxel, docetaxel, gemcitabine, vinorelbine.
[c]Patients who have been administered chemotherapy drugs other than paclitaxel, docetaxel, gemcitabine, vinorelbine.

observed that tumor cells which metastasized to bone in patients with breast cancer were more likely to overexpressed IL-11. And this overexpressed IL-11 was a poor prognostic indicator. In our study, there was no significant change in serum IL-11 levels before and after the chemotherapy in PDGV group ($P = .821$) while there was a significant decrease in the

Table 2. Laboratory measurements before and after the chemotherapy treatment.

	THE PDGV TREATMENT GROUP[a] (N = 21) X ± SD OR MED (IQR)[b]		THE OTHER TREATMENT GROUP[c] (N = 23) X ± SD OR MED (IQR)[b]		P_1	P_2
	BASELINE	FIRST DAY	BASELINE	FIRST DAY		
Hemoglobin (g/dL)	12.3 ± 1.7	12 ± 1.8	12.3 ± 1.5	12.1 ± 1.6	.312	.157
Hematocrit	37.4 ± 5.1	36.5 ± 5.4	37.4 ± 4	36 ± 5	.245	.013[d]
Blood urea nitrogen (mg/dL)	19 ± 6.6	20.3 ± 6.1	17.9 ± 5.1	18.3 ± 5.9	.457	.820
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.1	.695	.389
AST (UI/L)	20 ± 10	27 ± 13	21 (16-28)	22 (20-30)	.034[d]	.197
ALT (UI/L)	18 ± 14	23 ± 17	17 (14-34)	21 (15-34)	.136	.235
GGT (UI/L)	60 ± 58	60 ± 66	25 (17-41)	34 (20-100)	.652	.455
Total protein (mg/dL)	6.9 ± 0.4	7 ± 0.4	6.9 ± 0.6	6.9 ± 0.6	.567	.082
Albumin (mg/dL)	3.6 ± 0.4	3.6 ± 0.4	3.9 ± 0.3	3.8 ± 0.5	.794	.030[d]
Spot urine density	1017 ± 5	1014 ± 7	1014 ± 6	1014 ± 6	.349	1.00
Serum osmolality	283 ± 9	278 ± 5	281 ± 13	277 ± 6	.040[d]	.634
Urine osmolality	927 ± 335	953 ± 355	871 ± 403	890 ± 373	.643	.876
Sedimentation	56 ± 291	52 ± 33	41 ± 28	47 ± 38	.296	.148
Complement (g/L)						
C3	1.7 (1.3-133)	1.8 (1.4-131)	64 ± 73	54 ± 71	.551	.775
C4	0.4 (0.3-28)	0.4 (0.3-30)	12 ± 15	13 ± 17	.280	.785
Immunoglobulin (g/L)						
G	18 (15-1084)	17 (14-1105)	563 ± 678	555 ± 62	.363	.858
A	3.3 (2.5-198)	4.1 (2.2-181)	95 ± 116	102 ± 122	.842	.622
M	1.2 (0.9-90)	1.6 (0.9-101)	56 ± 67	47 ± 62	.426	.774
Serum protein electrophoresis (%)						
Alb	48.4 ± 7	47.8 ± 6.3	51.4 ± 5.7	51.7 ± 6	.586	.353
α_1	6.6 ± 1.8	6.7 ± 1.5	6 ± 2	5.8 ± 2.3	.196	.679
α_2	15 ± 3	14.6 ± 3	13.1 ± 4.9	13 ± 5	.117	.887
β_1	5.3 ± 0.8	5.4 ± 0.7	6.2 ± 0.8	5.9 ± 0.7	.266	.080
β_2	6.2 ± 1	6.2 ± 0.9	6 ± 0.9	6.2 ± 0.8	.334	.453
γ	18.5 ± 4.3	19.2 ± 3.9	17.3 ± 3.8	17.3 ± 3.8	.249	.492

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; PDGV, paclitaxel, docetaxel, gemcitabine, or vinorelbine.
P_1 denotes difference before and after the treatment in the PDGV group. P_2 denotes difference before and after the treatment in the other treatment group.
[a]Patients who have been administered any of the paclitaxel, docetaxel, gemcitabine, and vinorelbine.
[b]X ± SD: mean ± standard deviation. Med (IQR): median ± interquartile range.
[c]Patients who have been administered chemotherapy drugs other than paclitaxel, docetaxel, gemcitabine, and vinorelbine.
[d]*P*-value < .05 was accepted as statistically significant.

Table 3. Clinical measurements and symptoms before and after the chemotherapy treatment.

	THE PDGV TREATMENT GROUP[a] (N = 21) X ± SD[b]		THE OTHER TREATMENT GROUP[c] (N = 23) X ± SD		P_1	P_2
	BASELINE	FIRST DAY	BASELINE	FIRST DAY		
Body weight (kg)	68.4 ± 11.2	69.1 ± 11.4	70.6 ± 11.6	71.2 ± 12	.000[d]	.028[d]
Leg circumference (cm)						
Right	24 ± 3.3	24.5 ± 3.6	24.7 ± 1.8	25.2 ± 1.9	.125	.054
Left	24 ± 3.2	24.3 ± 3.5	24.5 ± 1.7	24.8 ± 1.8	.079	.038[d]
Blood pressure (mmHg)						
Systolic	109 ± 11	116 ± 14	121 ± 15	120 ± 16	.025[d]	.928
Diastolic	69 ± 8	71 ± 9	75 ± 9	75 ± 9	.331	1.00
Pulse (beat/min)	79 ± 13	80 ± 9	75 ± 9	75 ± 9	.519	.745
Weakness	—	1	—	1	—	—
Shortness of breath	—	4	—	4	—	—
Cough	—	3	—	4	—	—
Hoarseness	—	2	—	1	—	—
Skin rash	—	2	—	1	—	—
Muscle and joint pain	—	1	—	1	—	—

Abbreviation: PDGV, paclitaxel, docetaxel, gemcitabine, or vinorelbine.
P_1 denotes difference before and after the treatment in the PDGV group. P_2 denotes difference before and after the treatment in the other treatment group.
No one had the fever, voice misery, and rash-itch on the skin before and after receiving the chemotherapy.
[a]Patients who have been administered any of the paclitaxel, docetaxel, gemcitabine, vinorelbine.
[b]X ± SD: mean ± standard deviation.
[c]Patients who have been administered chemotherapy drugs other than paclitaxel, docetaxel, gemcitabine, and vinorelbine.
[d]*P*-value < .05 was accepted as statistically significant.

Table 4. Cytokine levels on the baseline and the first day following chemotherapy.

	THE PDGV TREATMENT GROUP[a] (N = 21) X ± SD OR MED (IQR)[b]		THE OTHER TREATMENT GROUP[c] (N = 23) X ± SD OR MED (IQR)[b]		P_1	P_2
	BASELINE	FIRST DAY	BASELINE	FIRST DAY		
VEGF (pg/mL)	310 ± 185	309 ± 207	149 ± 146	146 ± 155	.968	.896
TNF (pg/mL)	14.3 (11.3-28.0)	20.5 (11.0-31.3)	19 ± 10	21 ± 11	.741	.421
IL-2 (pg/mL)	1.3 (0.1-27.6)	0.1 (0.1-13.6)	30 ± 46	25 ± 50	.422	.720
IL-11 (pg/mL)	26.8 (4.5-120.2)	45.6 (11.2-103.9)	68.1 (7.2-219.7)	24.2 (5.3-76.5)	.821	.006[d]

Abbreviations: IL, Interleukin; PDGV, paclitaxel, docetaxel, gemcitabine, or vinorelbine; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.
P_1 denotes difference before and after the treatment in the PDGV group. P_2 denotes difference before and after the treatment in the other treatment group.
[a]Patients who have been administered any of the paclitaxel, docetaxel, gemcitabine, and vinorelbine.
[b]X ± SD: Mean ± standard deviation. Med (IQR): median ± interquartile range.
[c]Patients who have been administered chemotherapy drugs other than paclitaxel, docetaxel, gemcitabine, and vinorelbine.
[d]*P*-value < .05 was accepted as statistically significant.

other treatment arm ($P = .006$). We could not find any relation between the prognosis and levels of IL-11 in both groups in 8 months. This result in our study is thought to be due to the short follow-up period and the low number of cases. As with other cytokines, there was also no correlation between serum IL-11 levels and the symptoms of the patients. Maybe the reason was that 15 of 44 patients (34% of all patients) received adjuvant chemotherapy in our patient group, while the recent

studies have stated that serum cytokine levels correlate with tumor burden.[22-29] Since the number of patients was low, and 34% of all patients received adjuvant chemotherapy, it could not be detected any significant difference in serum IL-2, TNF, VEGF levels, and accordingly the symptoms.

No relationship between the serum cytokine levels and the symptoms and signs after the chemotherapy treatments arose from the short serum half-lives of cytokines.[4,30,31] Therefore, we could not catch the peak of serum cytokines levels at the 24th hour of the treatment. We observed "shortness of breath that develops after 12 h of chemotherapy and lasts for about half an hour" in three patients who received vinorelbine in the PDGV group. That can be explained by the short serum half-lives of these cytokines. In this respect, for an objective assessment, the serum cytokine levels in those patients may need to be assessed with serum samples taken every 15 min after treatment. It is clear that the application of this working order would not be suitable for a clinical trial on humans.

There was also no correlation between changes in serum cytokine levels, symptoms and signs, and response to the chemotherapy treatment protocols in our study. This result can be dependent on three parameters: the heterogeneous patient group for the cancer types, the malign cell burdens, and the heterogeneous treatment protocols. When it was looked at the previous studies, if a study group was composed of heterogeneously patient groups in terms of these parameters, it was reported that there is no relationship between the changes in serum cytokine levels and these parameters, and vice versa.[32,33] It is seen that the low number of patients was in our study, as well as the heterogeneous patient group for cancer type and treatment protocols. The fairly high standard deviation values of serum VEGF, TNF-α, IL-2, and IL-11 were the most important indicator that patient heterogeneity greatly influenced the results of our study. The reason for the heterogeneity of our patient group was that all patients were chosen randomly at the outpatient and inpatient clinics.

VEGF level in circulation is consisted of VEGF released from tumor tissue, as well as VEGF released from platelets or leukocytes during normal blood clotting. One of the important points to note is that the majority of the previous studies evaluated the VEGF levels in frozen tumor tissue, tumor cytosol, or paraffin embedded tumor tissues[34-37] not in the serum samples. As can be expected, VEGF level is the higher in the hypoxic tumor tissue and its neighboring tissues than the serum. However, we measured the VEGF levels in serum samples in our study. If a study in which VEGF level was measured in serum sample, similar to our study, the increased in circulating VEGF levels was particularly associated with large tumor burden and metastatic disease.[23,28,29,38] All of the breast cancer patients in our study received adjuvant chemotherapy (VEGF-releasing tumor tissue is theoretically absent). Therefore, it was not surprising that our patients serum VEGF levels were lower than the similar previous studies.[23,28,29,34-38] There was also no significant changes in serum VEGF levels before and 24 h after the chemotherapy treatment.

When it is looked at the previous publications about the levels of complement and immunoglobulin in cancer patients, the pre-chemotherapy treatment period has been evaluated to find out whether there is a relation between these marker levels and the prognosis. One of the exception of these previous studies, Tsavaris et al[19] evaluated levels of complement and immunoglobulin in 100 colorectal cancer patients at pre and post period of the receiving chemotherapy treatment. They detected increasing IgG and IgM levels before the chemotherapy treatment was correlated with prolonged life-span.[19] In our study, we evaluated the differences in Ig and complement levels before and 24 h after the first cycle of the first chemotherapy treatment. In our study, there was no difference between immunoglobulin and complement levels in pre-chemotherapy and post-chemotherapy treatment periods, either in the lung cancer group or in the other group which includes the patients with breast cancer. In addition, there was no correlation between Ig and complement levels and prognosis. The patient group who had adjuvant chemotherapy treatment (who had no tumor tissue is theoretically) was not considered responsible for this result, because 29 patients (65.9%) who had neoadjuvant treatment had also the same result.

Previous studies have shown that there is a triad becoming of hypotension, hemoconcentration, and serum hypoalbuminemia in the systemic capillary leak syndrome.[4] We did not detect any systemic capillary leak syndrome case in our patient group. After the treatment, we identified some symptoms and signs only. However, we hypothesized that the pathophysiology of the symptoms and signs (generalized edema, hypotension, shortness of breath, fatigue, widespread muscle and joint pain, numbness, and skin rash) can have similar pathophysiology of this syndrome. We look at this aspect, the differences between the results of our study and the previous studies may arose the characteristics of the patient groups (cancer type, treatment protocols, and the tumor burden).[4-6] In our study, the systolic blood pressure was increased ($P = .032$) after taking the treatment in PDGV group while the diastolic blood pressure was not changed ($P = .286$) in the same group. The albumin level, and serum and urine osmolarity were not changed before and after the treatment in both groups.

In the present study, we could not determined any correlation between the serum cytokine levels, symptoms and signs, chemotherapy response, and chemotherapeutic drugs which is thought to be responsible for capillary leak follow-up the chemotherapy treatment. We also did not detect any systemic capillary leak syndrome because the syndrome is appeared very rare and our case number was low. We did not detect any significant change of the serum IL-2, TNF, and VEGF levels before and after the treatment. The result could be dependent on the small sample size and the short half-life of cytokine. We collected the serum samples before and 24 h after the

chemotherapy treatment, so we could not catch the peak-time of these cytokines.

Conclusions

The topic is a current topic between the clinicians. These symptoms and life-threatening syndrome is a sudden and unexplained leakage of plasma into the tissues. It can appear in patients who have heart disease, lung disease, kidney disease, and hypothyroidism. It can appear in patients who take a chemotherapy treatment, too. If a chemotherapy treatment contains paclitaxel, docetaxel, gemcitabine, or vinorelbine, these symptoms and signs can occur more often than the chemotherapy treatment not containing these drugs, but the pathophysiology is still not clear. In this study, there was no association between edema, dyspnea, cough, flu-like symptoms, and signs suggesting the cytokine effect associated with the chemotherapy drugs administered. According to the group receiving PDGV treatment, there was a significant decrease in IL-11 levels ($P = .006$) in the other treatment group, but no correlation was found between the drugs applied and the mentioned symptoms, the chemotherapeutic response, the level of serum TNF, IL-2, L-11, and VEGF. The result could be dependent on the small sample size and the short half-life of cytokine. However, this study can raise awareness about this topic, and it can lead to larger and well-planned studies.

Author Contributions

Study concept and design: AD, HK
Acquisition of data: HK
Analysis and interpretation of data: AD, HA, HK, BY
Drafting of the manuscript: HK, AD, KC, BY
Critical revision: HK, AD, BY, KC

ORCID iD

Havva Keskin https://orcid.org/0000-0003-1794-4473

REFERENCES

1. Demirkazik A, Icli F. *Tıbbi Onkoloji*. Ankara: Antıp Press; 2005: 85–101.
2. Griffon-Etienne G, Boucher Y, Brekken C, et al. Taxane-induced apoptosis decompresses blood vessels and lowers interstitial fluid pressure in solid tumors: clinical implications. *Cancer Res*. 1999;59:3776–3782.
3. Roth J, Souza GP. Fever induction pathways: evidence from responses to systemic or local cytokine formation. *Braz J Med Biol Res*. 2001;34:301–314. doi:10.1590/s0100-879×2001000300003.
4. Xie Z, Chan E, Yin Y, et al. Inflammatory markers of the systemic capillary leak syndrome (Clarkson Disease). *J Clin Cell Immunol*. 2014;5:1000213. doi:10.4172/2155-9899.1000213.
5. Druey KM, Greipp PR. Narrative review: the systemic capillary leak syndrome. *Ann Intern Med*. 2010;153:90–98. doi:10.7326/0003-4819-153-2-201007200-00005.
6. Gousseff M, Arnaud L, Lambert M, et al. The systemic capillary leak syndrome: a case series of 28 patients from a European registry. *Ann Intern Med*. 2011;154:464–471. doi:10.7326/0003-4819.
7. Bajwa R, Starr J, Daily K. Gemcitabine-induced chronic systemic capillary leak syndrome. *BMJ Case Rep*. 2017. doi:10.1136/bcr-2017-221068.
8. Gardini AC, Aquilina M, Oboldi D, et al. Separate episodes of capillary leak syndrome and pulmonary hypertension after adjuvant gemcitabine and threeyears later after nab-paclitaxel for metastatic disease. *BMC Cancer*. 2013;13:542. doi:10.1186/1471-2407-13-542.
9. Gmiński J, Mykała-Cieśla J, Machalski M, et al. Immunoglobulins and complement components levels in patients with lung cancer. *Rom J Inter Med*. 1992;30:39–44.
10. Vinzenz K, Pavelka R, Schönthal E, Zekert F. Serum immunoglobulin levels in patients with head and neck cancer (IgE, IgA, IgM, IgG). *Oncology*. 1986;43:316–322. doi:10.1159/000226390.
11. Peng RQ, Ding Y, Zhang X, Liao Y, Zheng LM, Zhang XS. A pilot study of paclitaxel combined with gemcitabine followed by interleukin-2 and granulocyte macrophage colony-stimulating factor for patients with metastatic melanoma. *Cancer Biol Ther*. 2012;13:1443–1448. doi:10.4161/cbt.22005.
12. Lesterhuis WJ, Rennings AJ, Leenders WP, et al. Vascular endothelial growth factor in systemic capillary leak syndrome. *Am J Med*. 2009;122:e5–e7. doi:10.1016/j.amjmed.2009.01.020.
13. Kai-Feng W, Hong-Ming P, Hai-Zhou L, Li-Rong S, Xi-Yan Z. Interleukin-11-induced capillary leak syndrome in primary hepatic carcinoma patients with thrombocytopenia. *BMC Cancer*. 2011;11:204. doi:10.1186/1471-2407-11-204.
14. Phaibulvatanapong E, Srinonprasert V, Ithimakin S. Risk factors for chemotherapy-related toxicity and adverse events in elderly Thai cancer patients: a prospective study. *Oncology*. 2017;94:149–160. doi:10.1159/000485078.
15. Mier JW, Vachino G, van der Meer JWM, et al. Induction of circulating tumor necrosis factor (TNF-α) as the mechanism for the febrile response to interleukin-2 (IL-2) in cancer patients. *J Clin Immunol*. 1988;8:426–436. doi:10.1007/bf00916947.
16. Amoura Z, Papo T, Ninet J, et al. Systemic capillary leak syndrome: report on 13 patients with special focus on course and treament. *Am J Med*. 1997;103:514–519. doi:10.1016/S0002-9343(97)00272-6.
17. Barlesi F, Villani P, Doddoli C, Gimenez C, Kleisbauer JP. Gemcitabine-induced severe pulmonary toxicity. *Clin Pharmacology*. 2004;18:81. doi:10.1046/j.0767-3981.2003.00206.x.
18. Dimopoulou I, Bamias A, Lyberopoulos P, Dimopoulos MA. Pulmonary toxicity from novel antineoplastic agents. *Annals of Oncol*. 2005;10:1093–1099. doi:10.1093/annonc/mdj057.
19. Tsavaris N, Tsigalakis D, Bobota A, et al. Prognostic value of serum levels of immunoglobulins (IgA, IgM, IgG, IgE) in patients with colorectal cancer. *Eur J Surg Oncol*. 1992;18:31–36.
20. Kawabe S, Saeki T, Yamazaki H, Nagai M, Aoyagi R, Miyamura S. Systemic capillary leak syndrome. *Intern Med*. 2002;41:211–215. doi:10.2169/internalmedicine.41.211.
21. Berry J, Singh B, Lucci A. Cox-2 induces interleukin-11 production in human breast cancer cells. *Journal of Surgical Research*. 2004;121:427. doi:10.1016/j.jss.2004.07.195.
22. Eide HA, Knudtsen IS, Sandhu V, et al. Serum cytokine profiles and metabolic tumor burden in patients with non-small cell lung cancer undergoing palliative thoracic radiation therapy. *Adv Radiat Oncol*. 2018;3:130–138. doi:10.1016/j.adro.2017.12.007.
23. Karayiannakis AJ, Bolanaki H, Syrigos KN, et al. Serum vascular endothelial growth factor levels in pancreatic cancer patients correlate with advanced and metastatic disease and poor prognosis. *Cancer Lett*. 2003;194:119–124. doi:10.1016/s0304-3835(03)00047-8.
24. Kraft A, Weindel K, Ochs A, et al. Vascular endothelial growth factor in the sera and effusions of patients with malignant and nonmalignant disease. *Cancer*. 1999;85:178–187.
25. Yamamoto Y, Toi M, Kondo S, et al. Concentration of vascular endothelial growth factor in the sera of normal controls and cancer patients. *Clin Cancer Res*. 1996;2:821–826.
26. Yamamoto S, Konishi I, Mandai M, et al. Expression of vascular endothelial growth factor (VEGF) in epithelial ovarian neoplasms: correlation with clinicopathology and patient survival, and analysis of serum VEGF levels. *Br J Cancer*. 1997;76:1221–1227.
27. Fujisaki K, Mitsuyama K, Toyonaga A, Matsuo K, Tanikawa K. Circulating vascular endothelial growth factor in patients with colorectal cancer. *Am J Gastroenterol*. 1998;93:249–252.
28. Chin KF, Greenman J, Gardiner E, Kumar H, Topping K, Monson J. Pre-operative serum vascular endothelial growth factor can select patients for adjuvant treatment after curative resection in colorectal cancer. *Br J Cancer*. 2000;83:1425–1431. doi:10.1054/bjoc.2000.1508.
29. Davies MM, Jonas SK, Kaur S, Allen-Mersh TG. Plasma vascular endothelial but not fibroblast growth factor levels correlate with colorectal liver metastasis vascularity and volume. *Br J Cancer*. 2000;82:1004–1008. doi:10.1054/bjoc.1999.1033.
30. Whiteside TL. Cytokines and cytokine measurements in a clinical laboratory. *Clin Diagn Lab Immunol*. 1994;1:257–260.
31. Aziz N, Detels R, Quint JJ, Li Q, Gjertson D, Butch AW. Stability of cytokines, chemokines and soluble activation markers in unprocessed blood stored under different conditions. *Cytokine*. 2016;84:17–24. doi:10.1016/j.cyto.2016.05.010.
32. Poon RT, Fan ST, Wong J. Clinical implications of circulating angiogenic factors in cancer patients. *J Clin Oncol*. 2001;19:1207–1225. doi:10.1200/jco.2001.19.4.1207.
33. Brattstrom D, Bergqvist M, Larsson A, et al. Basic fibroblast growth factor and vascular endothelial growth factor in sera from non-small cell lung cancer patients. *Anticancer Res*. 1998;18:1123–1127.
34. Ghosh S, Sullivan CO, Zerkowski MP, et al. High levels of vascular endothelial growth factor and its receptors (VEGFR-1, VEGFR-2, neuropilin-1) are

associated with worse outcome in breast cancer. *Hum Pathol*. 2008;39:1835–1843. doi:10.1016/j.humpath.2008.06.004.
35. Takahashi Y, Kitadai Y, Bucana CD, Cleary KR, Ellis LM. Expression of vascular endothelial growth factor and its receptor, KDR, correlates with vascularity, metastasis, and proliferation of human colon cancer. *Cancer Res*. 1995;55:3964–3968.
36. Ozdemir F, Akdogan R, Aydin F, et al. The effects of VEGF and VEGFR-2 on survival in patients with gastric cancer. *J Exp Clin Cancer Res*. 2006;25:83–88.
37. Itakura J, Ishiwata T, Shen B, Kornmann M, Korc M. Concomitant over-expression of vascular endothelial growth factor and its receptors in pancreatic cancer. *Int J Cancer*. 2000;85:27–34. doi:10.1002/(sici)1097-0215(20000101)85.
38. Valković T, Babarović E, Lučin K, et al. Plasma levels of osteopontin and vascular endothelial growth factor in association with clinical features and parameters of tumor burden in patients with multiple myeloma. *Biomed Res Int*. 2014;w2014:513170. doi:10.1155/2014/513170.