Orjinal Araştırma **Van Sağ. Bil. Derg.** *2024; 17(3):159-165.*
Original Research *https://doi.org/10.52976/vansaglik.1547450*

Investigation of Herpes Viridae and Parvovirus B19 Frequencies in Lymphopenic Malignant Patients Receiving Chemotherapy

Kemoterapi Alan Lenfopenik Malign Hastalarda Herpes Viridae ve Parvovirus B19 Sıklıklarının Araştırılması

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Cited: Kılıç A.F, Tekin S.B. (2024). Investigation of Herpes Viridae and Parvovirus B19 Frequencies in Lymphopenic Malignant Patients Receiving Chemotherapy. *Van Sağlık Bilimleri Dergisi*, 17(3), 159-165.

ABSTRACT

Objective: In this study, we aimed to investigate the incidence of Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Cytomegalovirus (CMV) and Parvovirus B19 viral infections in patients diagnosed with cancer receiving chemotherapy in our clinic.

Material and Method: In this study, 138 lymphopenic patients who were hospitalized and received chemotherapy at Medical Oncology Clinic between April 2018 and July 2018 were evaluated prospectively. Cancer diagnoses of the patients included in the study were lung, esophagus, prostate, breast, pancreatic, colorectal, stomach, brain and nervous system, ovarian cancer and other (ewing sarcoma, hepatocellular carcinoma, larynx carcinoma, bladder carcinoma, malignant mesenchymal tumor, multiple myeloma, lymphoma, metastatic carcinoma of unknown primary, renal cell carcinoma, cervical carcinoma, testicular carcinoma) cancers. The patients were at various stages of cancer, had various histological subtypes, and were receiving various chemotherapies. The % frequency of EBV, HSV, CMV and Parvovirus B19 in serum samples were determined.

Results: The meanage of the patients was 58.93 ± 13.28 years, and the mean duration of diagnosis was 2,0 ± 2,2 years. EBV the polymerase chain reaction (PCR) positivity was detected in 9 patients (6.5%), CMV PCR positivity in 12 patients (8.7%) and EBV and CMV (together) PCR positivity in 1 (0.7%) patient. HSV and parvovirus B19 PCR positivity were not determined in any patients. According to the results of the survival analysis, the average survival time in all lymphopenic patients was 3.71 months. It was observed that 65.21% of all lymphopenic patients die within 12 months following lymphopenia diagnosis.

Conclusion: As a result of our study, EBV and CMV PCR positivity rates were determined in all lymphopenic patients receiving chemotherapy (6.5% and 8.7%, respectively). More comprehensive studies are needed to determine the incidence of HSV and parvovirus B19. In addition, lymphopenic patients receiving chemotherapy should be followed up by physicians for viral infections and treated with antiviral therapy in the early stages of infection.

Keywords: *CMV, EBV, HSV, Lymphopenia, Parvovirus B19*

ÖZET

Giriş: Bu çalışmada kliniğimizde kemoterapi alan kanser tanısı almış hastalarda Epstein-Barr virüsü (EBV), Herpes simpleks virüsü (HSV), Sitomegalovirüs (CMV) ve Parvovirüs B19 viral enfeksiyonlarının sıklığını araştırmayı amaçladık.

Materyal ve Metot: u çalışmada Nisan 2018 ile Temmuz 2018 tarihleri arasında Tıbbi Onkoloji Kliniği'nde yatarak kemoterapi alan 138 lenfopenik hasta prospektif olarak değerlendirildi. Çalışmaya dahil edilen hastaların kanser tanıları akciğer, özofagus, prostat, meme, pankreas, kolorektal, mide, beyin ve sinir sistemi, over kanseri ve diğer (Ewing sarkomu, hepatoselüler karsinom, larinks karsinomu, mesane karsinomu, malign mezenkimal tümör, multipl miyelom, lenfoma, primeri bilinmeyen metastatik karsinom, renal hücreli karsinom, servikal karsinom, testis karsinomu) kanserlerdi. Hastalar çeşitli kanser evrelerindeydi, çeşitli histolojik alt tiplere sahipti ve çeşitli kemoterapiler alıyorlardı. Serum örneklerinde EBV, HSV, CMV ve Parvovirus B19'un % sıklığı belirlendi.

Bulgular: Hastaların ortalama yaşı 58,93 ± 13,28 yıl, ortalama tanı süresi ise 2,0 ± 2,2 yıldı. EBV polimeraz zincir reaksiyonu (PCR) pozitifliği 9 hastada (%6,5), CMV PCR pozitifliği 12 hastada (%8,7) ve EBV ve CMV (birlikte) PCR pozitifliği 1 hastada (%0,7) tespit edildi. HSV ve parvovirus B19 PCR pozitifliği hiçbir hastada belirlenmedi. Sağkalım analizi sonuçlarına göre tüm lenfopenik hastalarda ortalama sağkalım süresi 3,71 ay idi. Tüm lenfopenik hastaların %65,21'inin lenfopeni tanısı konulduktan sonraki 12 ay içinde öldüğü gözlemlendi.

Sonuç: Çalışmamızın sonucunda, kemoterapi alan tüm lenfopenik hastalarda EBV ve CMV PCR pozitifliği oranları belirlendi (sırasıyla %6,5 ve %8,7). HSV ve parvovirüs B19 insidansını belirlemek için daha kapsamlı çalışmalara ihtiyaç vardır. Ayrıca, kemoterapi alan lenfopenik hastalar viral enfeksiyonlar açısından hekimler tarafından takip edilmeli ve enfeksiyonun erken evrelerinde antiviral tedavi ile tedavi edilmelidir.

Anahtar kelimeler: *CMV, EBV, HSV, Lenfopeni, Parvovirus B19*

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Received: 10.09.2024, Accepted: 24.12.2024 and Pubished:30.12.2024

INTRODUCTION

here exist two major deadly situations patients regularly encounter during the terminal phase of cancer: infections and bleeding (Abou Dagher et al., 2017; Zaorsky et al., 2017). The incidence of infectious diseases has increased in cancer patients, and the addition of infectious diseases to the cancer symptoms is an important cause of morbidity and mortality. In particular, the addition of viral infections to the existing clinical situation in lymphopenic cancer patients adversely affects the treatment prognosis. Infections may be bacterial, viral, and fungal. It has been reported that 2.2 million of the 14 million new cancer cases recorded all over the world in 2012 were caused by infectious agents, and approximately 12% of worldwide cancer cases were associated with viral infections (Plummer et al., 2016). Although bacterial and fungal infections can be detected somewhat more easily, experience and detailed information are required to detect viral infections, particularly sepsis (Kochanek et al., 2019). Lymphopenia is a situation characterized by having a number of lymphocytes less than 1,500/μL (Oliveira & Fleisher, 2010). Lymphocytes play an important role as immune effector cells during immunosurveillance in cancer patients (Galon et al., 2013). Lymphopenia, particularly developed during the terminal cancer period, causes lymphopenia-related infections (Miyoshi et al., 2020). Furthermore, chemotherapeutics may show a lymphopenic effect (Kroese et al., 2021). Therefore, in this study, we aim to draw attention to this occurrence in cancer patients by determining the incidence of the viral infections and to contribute to the survival and treatment of the patients with the results obtained.

The most serious morbidity results from active infections are induced by members of the herpes virus family. Herpes simplex virus and varicella zoster virus infections have been observed in almost all types of cancer patients (Jehn, 1988). In contrast, cytomegalovirus infections can cause life-threatening morbidity in patients with bone marrow transplantation (Boeckh et al., 2003). The antiviral agents that can be used against these pathogens may reduce the morbidity and mortality (Yahav et al., 2009). Treatment of these infections depends on the control of malignancy and the ability of the patient to establish an adequate immune response (Johnson & Roodman, 1989).

After neutropenia, the most important cause of immunosuppression in cancer patients is lymphopenia (Kitayama et al., 2010). These viruses are known to cause lymphopenia and also increase the lymphocyte destruction in lymphopenic patients. The cellular immunity plays a key role in the control of the infections and developments of the symptoms caused by herpes viruses and Parvovirus B19. The number of circulating lymphocytes is a positive predictor of tumor response in chemoradiotherapy (Forman et al., 2017).

In this study, we aimed to determine the DNA levels of HSV, CMV, EBV, and Parvovirus B19 and uncover their viral capacity and thus determine the incidence of viral infections in cancer patients with lymphopenia receiving chemotherapy.

MATERIAL and METHOD

Ethics Committee permission was obtained from local ethics committee with the decision dated 15.02.2018, numbered 02-51. Patient information was obtained retrospectively from the hospital data processing system after the decision of the local ethics committee.

In this study, we included a total of 138 lymphopenic cancer patients receiving chemotherapy and hospitalized in a medical oncology clinic between April 2018 and July 2018. We then informed those who met the criteria for inclusion in the study of their eligibility and included them in the study after obtaining their consent.

We included a total of 138 lymphopenic patients in the study. The inclusion criteria were being diagnosed with cancer, receiving or had received chemotherapy, being lymphopenic (the number of lymphocytes< 1.5× 103 cells/mm3) and being between the ages of 18 and 85. The exclusion criteria were having a chronic disease other than cancer, being pregnant, breast-feeding, and being aged<18 or >85.

We did not examine lymphocyte subtypes such as CD4, CD8, and NK cells before and during the study. The patients were at various stages of cancer, had various histological subtypes, and were receiving various chemotherapies. The patients included in the study did not have any clinical manifestations of viral infections, and they were not compared in terms of cancer stages, cancer subtypes, and types of chemotherapy received.

We took 4 ml of venous blood samples from all patients and kept the samples at room temperature for almost 30 min. We obtained the serum in the medical microbiologylaboratory of

Ataturk University Hospital (centrifuged at 4.000 RPM for 5 min, then we extracted the supernatant part). We determined the lymphocyte count on the hemogram device. In terms of the lymphocyte count, we accepted the patients between 0.5–1.0× 103 cells/mm3 as having mild to moderate lymphopenia, and we accepted the ones between <0.5 × 103 cells/mm3 as having severe lymphopenia. In the serum samples of all the patients, we determined the presence of EBV, HSV, CMV and parvovirus B19 through commercial kits and the polymerase chain reaction (PCR).

We performed statistical analyses using SPSS version 23.0 (SPSS, Chicago). We made descriptive statistics using percentage frequency, mean±standard deviation, and min-max values. We made comparisons between male and female patients with an independent samples t-test. We performed survival analyses using Kaplan-Meier analysis and considered P values of <0.05 at the 95% confidence interval as statistically significant.

RESULTS

We investigated a total of 138 patients with lymphopenia diagnosed with carcinoma for the presence of the EBV, HSV, CMV and parvovirus B19 infectious agents. There was no statistically significant difference between male and female patients in terms of age (p=0.155). The mean duration of diagnosis of the patients was 2.0 ± 2.2 years (Table 1).

Table 1. Demographic data of the patients

Patients	Age (Years)	*P* Value
All Patients (*n*=138)	58.93 ± 13.28 (19–85)	0.155
Female Patients (*n*=58)	57.03 ± 13.83 (19–77)	
Male Patients (*n*=80)	60.30 ± 12.79 (19–85)	

Results are given as mean±standard deviation (min-max). P: Independent group comparison (female patients vs. male patients) test statistic *p* value.

Table 2 summarizes the distribution of EBV, CMV, HSV, and parvovirus B19 positivity percentages by gender, and Table 3 illustrates the lymphocyte, EBV, and CMV counts of patients. We observed the coexistence of EBV and CMV in 0.7% of all lymphopenic patients and 3.2% of severe lymphopenic patients (Figure 1).

The Kaplan-Meier survival analysis revealed the mean survival timeswere 3.71 monthsin all lymphopenic patients; 3.08 monthsin mild–moderate lymphopenic patients; and 3.91 months in severe lymphopenic patients. In terms of survival, the difference between the degree of lymphopenia was not statistically significant (p=0.738). Mortality rates within 12 months following the lymphopenia diagnosis were 65.21% in all lymphopenic patients, 64.48% in mild–moderate lymphopenic patients, and 67.74% in severe lymphopenic patients.

Table 2. Distribution of Epstein-Barr virus, cytomegalovirus, herpes simplex virus and parvovirus B19 percentage of positivity by gender

Virus Type	All Patients (*n*=138)	Female Patients (*n*=58)	Male Patients (*n*=80)	*P* Value
EBV (+); *n* (%)	14 (10.1)	7 (12.1)	7 (8.8)	0.505
CMV (+); *n* (%)	13 (9.4)	5 (8.6)	8 (10.0)	0.368
HSV (+); *n* (%)	0 (0)	0 (0)	0 (0)	
Parvovirus B19 (+); *n* (%)	0 (0)	0 (0)	0 (0)	

EBV: Epstein-Barr virus, CMV: Cytomegalovirus, HSV: Herpes simplex virus, P: Independent group comparison (female patients vs. male patients) test statistic *p*-value

Table 3. Lymphocyte, Epstein-Barr virus and cytomegalovirus counts of patients

Counts	All Patients (*n*=138)	Female Patients (*n*=58)	Male Patients (*n*=80)	*P* Value
Lymphocyte Counts (× 10^3 cell/mm^3)	0.67± 0.24 (0.10–0.99)	0.71±0.22 (0.14–1.00)	0.64±0.24 (0.10–0.99)	0.088
EBV (Copy/mL)	303.74±1.720.69 (0.00–13.300)	196.95±1.208.31 (0.00–9.154)	381.16±2.016.59 (0.00–13.300)	0.505
CMV (Copy/mL)	562.49±3.429.46 (0.00–29.490)	896.88±4.321.16 (0.00–29.490)	320.06±2.604.21 (0.00–23.270)	0.368

EBV: Epstein-Barr virus, CMV: Cytomegalovirus. Results are given as mean±standard deviation (min-max). P: Independent group comparison (female patients vs. male patients) test statistic *p* value

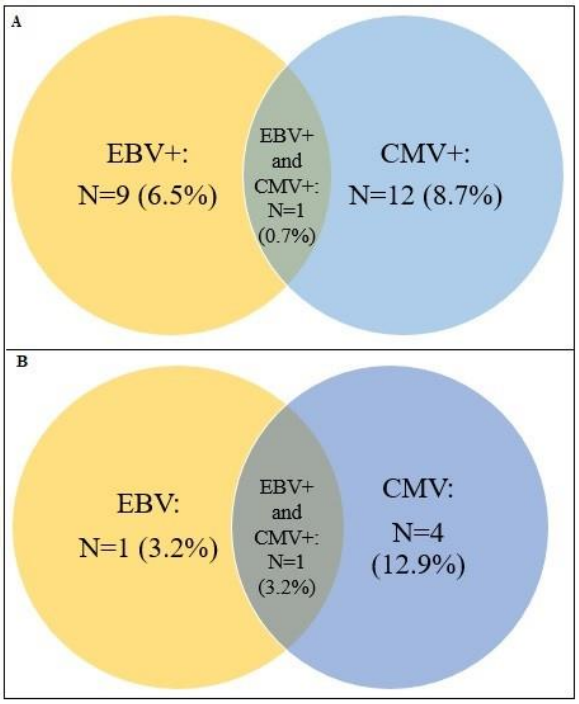

Figure 1. Coexistence of Epstein-Barr virus and Cytomegalovirus in Lymphopenic Patients and Severe Lymphopenic Patients

A: Coexistence of Viral Infections in All Lymphopenic Patients

B: Association of Viral Infections in Severe Lymphopenic Patients

DISCUSSION

In this study, we determined the incidence of viral infections (HSV, CMV, EBV, and parvovirus B19) viral load in lymphopenic cancer patients receiving chemotherapy. We observed the EBV PCR positivity in 9 (6.5%) patients, CMV PCR positivity in 12 (8.7%) patients, and EBV and CMV PCR positivities in 1 (0.7%) patient. We did not detect the HSV and parvovirus B19 PCR positivities in any patients.

Cancer is a condition in which the immune system cannot function sufficiently, and the immune system response is the prognostic factor. The most important element of the immune system is lymphocytes. Decreases in the lymphocyte level may lead to immune system insufficiency. The relationship between cancer and lymphopenia has been analyzed in various studies (Forman et al. 2017) and it has been shown lymphopenic patients show worse prognoses. The presence of lymphopenia before cancer treatment is an indicator of poor prognosis in patients with lung, breast, and colorectal cancers, as well as sarcoma and lymphoma (Forman et al. 2017). Moreover, pathological studies have shown survival rates are higher in patients with dense lymphocytic infiltration into solid tumors (Stowel et al. 2012). Recent studies have shown CD3+ and CD8+ lymphocyte infiltration densities are related to diversities in overall survival and disease-freetime. According to the tumor biopsy results, we found the intensive infiltration of these lymphocytes into tumor tissues are associated with tumor reduction preoperative chemotherapy and radiation therapy given before surgery. Although the extensive previous studies revealed the presence of lymphopenia before cancer treatment is associated with poor prognosis, the relationship of lymphopenia occurring after the surgery with the survival results was not systematically investigated.

The mortality rate within 12 months following the lymphopenia diagnosis was 65.21% in all patients, 64.48% in mild–moderate patients, and 67.74% in severe lymphopenic patients. In a study investigating the effects of lymphopenia on total survival rates, the overall survival rate in 12 months wasdetermined to be

almost 45% in lymphopenic patients with non-Hodgkin's lymphoma and almost 0% in patients with metastatic breast cancer, and almost 10% in patients with soft tissue sarcoma (Campian et al. 2013). In a study, the average survival rate was determined as 35% in 826 patients with lymphopenia (Martel et al. 2012). The survival rate of 32.26% determined in our study is close to the survival rate results of cancer patients with lymphopenia in the literature.

With the addition of lymphopenia to the mixed metabolic and hematological table in cancer patients, the susceptibility to fungal, bacterial, and viral infections increases. The increased susceptibility to viral infections in cancer patients negatively affects morbidity and mortality Colugnati et al. 2007).

The addition of viral infections to the lymphopenia and cancer, which already presents a severe clinical table, in cancer patients with lymphopenia, negatively affects the prognosis of the disease and treatment success. The viral infections observed are often the reactivations of asymptomatic latent infections and often cause respiratory tract infections. The most common viral infections observed in patients with cancer are CMV, HSV, EBV, and the varicella zoster virus, which are the community-acquired respiratory viruses. The most severe morbidity results from the active infection induced by members of the herpes virus family Sylwester et al. 2005). The diagnosis and treatment of the viral infections in cancer patients may be more difficult than those in non cancer patients. Therefore, the prevention and diagnosis of infection presence in cancer patients is vital.

In this study, 54.3% (n= 75 patients) of the patients with lymphopenia receiving chemotherapy had a history of blood transfusion. That there is a risk factor in blood transfusion in terms of viral infections should be taken into account (Lissoni et al. 2004). In our study, we found 10.7% of the patients with blood transfusion had EBV PCR positivity and 8.0% had CMV PCR positivity; 9.5% of the patients who did not have blood transfusion had EBV PCR positivity; and 11.1% had CMV PCR positivity. Therefore, in the patients in our study, the blood transfusion might have affected the incidence of CMV.

In this study, of all the patients, 6.5% had mild-moderate positive EBV infection, 7.5% of the severe patients with lymphopenia had positive EBV infection, and 3.2% of the patients with lymphopenia had EBV infection. Severely atypical lymphocytosis (decrease or dysfunction of more than 50% of lymphocytes) may be seen in EBV infection (Fleisher et al. 2004). EBV can infect host cells in the latent and lytic form.Various chemotherapeutic agents including cisplatin, 5-fluorouracil (5-FU) and paclitaxel can induce the transition of EBV infection in tumor cells from the latent form to lytic form (Dahlin et al. 2011). Although one study found the percentage of the patients using cisplatin, 5-FU, and paclitaxel was 55% (Dahlin et al. 2011), in our study we did not observe EBV PCR positivity. This may be due to the possibility that there was no EBV infection in the latent form or there was no latent-lytic transition in these patients.

EBV is related to post transplant lymphoproliferative disease (PTLD), which typically occurs after solid organ and stem-cell transplantation. Overall, 55–65% of all PTLD cases are reported to be caused by EBV Anitei et al. 2014). In this study, EBV infection was not detected because the number of the lymphogenic cancer patients with stem-cell transplantation was low (n=2 patients,1.4%).

The lymphopenia development in cancer patients is an important cause of morbidity and mortality. As a result of this study, 65.21% of all patients with lymphopenia died within 12 months following a diagnosis of lymphopenia. The mean time from lymphopenia diagnosis to death was 2.42±3.57 months. However, it was impossible to state the direct effect ofthelymphopeniaon life expectancyin cancer patients in this study because of the lack of a control group, including the non lymphopenic patients. We thus plan to determine life expectancy in non lymphopenic patients and compare our results in future studies.

One limitation of our study was the presence of patients with a chronic disease other than cancer, pregnancy, breast-feeding, age <18, and age >85. Again, our study has a relatively small sample size. studies with larger patient numbers will contribute more to the literature. It should also be kept in mind that there may be false positives/negatives in serum PCR results that may affect the interpretation. Also sample size (n = 138) of our study may not represent the broader population of lymphopenic cancer patients.

Conclusions

There was no statistically significant difference between male and female patients in terms of age (p=0.155). The mean duration of diagnosis of the patients was 2.0 ± 2.2 years. We observed the EBV PCR positivity in 9 (6.5%) patients, CMV PCR positivity in 12 (8.7%) patients, coexistence of EBV and CMV in 0.7% of all

lymphopenic patients and 3.2% of severe lymphopenic patients. To the best of our knowledge, following the literature search, this was the first study to investigate the incidences of HSV, CMV, EBV and parvovirus B19 together in lymphopenic cancer patients receiving chemotherapy. In conclusion, the number of lymphocytes must closely be observed for the early diagnosis of possible viral infections in cancer patients, especially in patients with severe lymphopenia, and antiviral prophylaxis approaches must be reviewed, if necessary.

Acknowledgment: This investigation and the research behind it would not have been possible without the exceptional support of dear professor Salim Başol Tekin and dear Professor Nurcan Kılıç Baygutalp.

Ethical Consent: Ethics committee approval was obtained from the local ethics committee with the decision dated 15.02.2018, reference number 02-51.

Authors' contributions: S.B.T idea/concept, critical review, references, control/supervısıon, fundings, and design. A.F.K data collection and processing, analysis and interpretation, literature review, writing the article, collecting materials.

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