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Investigation of the effect of chemotherapy on cytomegalovirus reactivity in patients with solid organ tumors

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ABSTRACT

Objectives: Chemotherapy induces an immunosuppressive state in patients with solid organ tumors. Cytomegalovirus (CMV) reactivation as a result of immunosuppression causes a severe clinical manifestation. However, in this group, CMV infections developing due to reactivation were not adequately discussed in the literature. The aims of this study were to determine the incidence of CMV reactivation after chemotherapy, to evaluate the contribution of chemotherapy to reactivation, to determine the incidence of asymptomatic and symptomatic infections and to investigate the results of the treatment.

Methods: A total of 93 patients with solid tumors were included in the study. Weekly blood samples were collected from the patients for three weeks before and after chemotherapy. Quantitative analysis of DNA was detected using CMV PCR kit (GeneProof CMV PCR kit, Bruno, Czech Republic). Diagnosis and treatment of patients were retrospectively reviewed.

Results: Of the patients, 65.6% were female and 34.4% were male. The mean age was 55 ± 12 years. The most common cancer types among the patients were breast cancer in 45.2%, lung cancer in 15.1%, and colon cancer in 12.9%. The mean leukocyte count of the patients was 7,647/mm3. CMV DNA was not detected in any patient. According to this result, none of the patients had CMV reactivation after chemotherapy.

Conclusions: In this study including patients with solid organ tumors with mild to moderate level of immunosuppression CMV DNA was not detected in any patient. Based on this finding no standard prophylaxis was required for CMV in this group of patients.

Keywords: Cytomegalovirus, solid organ tumor, chemotherapy

Cytomegalovirus (CMV) is the largest human herpes virus (HHV-5) that can remain latent in the body after acute infection. This virus can infect people of any age, which does not show seasonal or epidemic features for transmission. It causes widespread viral infection all over the world. It can be transmitted eas-

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ily from person to person. After the primary infection, the virus may remain latent and persistent in a wide variety of areas such as defense and epithelial cells. Infected individuals are an important source of virus scattering for a long time [1, 2].

In the United States and other developed countries, seroprevalence is 50%, while in developing countries this rate can reach 100% [3, 4]. In high-risk groups, seroprevalence can exceed 90%. CMV infection can be caused by CMV transmission (primary infection) and activation (reactivation) of latent infection due to immunosuppressive therapy. The primary infection is more benign and is seen more common in young ages. In addition to congenital infections, CMV reactivation may develop as a result of immunosuppressive treatment, usually in the period following solid organ, bone marrow or hematopoietic stem cell transplantation. CMV reactivation can present with severe clinical manifestations and the spectrum and severity vary according to the patient's serological status and the immunosuppressive treatment regimen selected. In particular, in oncology patients, chemotherapy and immunosuppressive CMV infection cause high morbidity and mortality [5]. The mortality of CMV infection which is reactivated in immunosuppressive patients is high [2, 6]. Therefore, when there are risk factors and clinical findings are suggestive of CMV infection in patients receiving chemotherapy, CMV reactivation should be considered and treatment should be applied accordingly [2, 7].

Chemotherapy-induced immunosuppression may also occur in patients with chemotherapy. However, in this group, risk of CMV reactivation was not clarified [8]. The aim of this study was to investigate the incidence of CMV reactivation after chemotherapy for solid tumors, to evaluate the contribution of chemotherapy to reactivation, to determine the incidence of asymptomatic and symptomatic infections.

METHODS

This prospective cross-sectional study was approved by the local ethics committee. Signed informed consent forms were taken from each participant.

Patients and Tests

A total of 93 patients with solid tumors were included in the study. The patients were seropositive for CMV (CMV IgG-positive). Blood samples were taken at baseline and then weekly during the chemotherapy and three weeks after chemotherapy were collected for CMV DNA study. DNA was isolated from the samples using the Hibrigen DNA isolation kit (GeneProof, Bruno, Czech Republic). Quantitative CMV DNA was detected using CMV PCR kit (GeneProof CMV PCR kit, Bruno, Czech Republic) in Rotor-Gene Q Real-time PCR instrument (Qiagen, Hilden, Germany). Blood count was studied every other that during the study. The leukocyte, lymphocyte and neutrophil values of the patients were analyzed using a particle-enhanced turbidimetric inhibition immunoassay method with Architect c8000 (Abbott Laboratories, Abbott Park, IL, USA) auto-analyzer. Other demographic data, diagnoses and treatments of the patients were retrospectively reviewed.

Statistical Analysis

Descriptive statistics were used to define the mean, standard deviation, minimum, median and maximum variables. Statistical significance level $p < 0.05$ was considered significant. The analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; 2013).

RESULTS

Of the patients, 65.6% were female and 34.4% were male. The mean age was 55 ± 12 years. The most common types of cancer among the patients were breast cancer in 45.2%, lung cancer in 15.1%, and colon cancer in 12.9%. The distribution and types of cancer and drugs used in the chemotherapy types are given in Table 1.

Distant metastases were detected in 29 (31.2%) patients. A total of 54 (58.1%) patients had a history of chronic disease other than malignancy, such as hypertension, chronic obstructive pulmonary disease, diabetes mellitus, hypothyroidism, and cerebrovascular accident. Sixty-seven (72%) patients underwent surgery and 13 (14.1%) patients underwent radiotherapy. Twelve (12.9%) patients had a permanent catheter

Table 1. Distribution of solid tumor patients and the drugs used

Diagnosis	n	%	Used chemotherapeutics
Breast cancer	42	45.2	5-fluorouracil (5-FU) based, Taxane-based, Anthracycline based
Lung cancer	14	15.1	Platinum-based, Taxane-based
Colon cancer	17	18.3	5-FU based, Platinum-based
Gastric cancer	4	4.3	5-FU based, Platinum-based
Cholangiocarcinoma	3	3.2	Platinum-based, Gemcitabine based, 5-FU based
Ovarian cancer	3	3.2	Taxane-based
Pancreatic cancer	3	3.2	Platinum-based
Bass-neck tumor	2	1.1	Platinum-based
Glioma	1	1.1	Irinotecan
Larynx tumor	1	1.1	Platinum-based
Bladder cancer	1	1.1	Platinum-based
Sarcoma	1	1.1	Anthracycline based
Testicular tumor	1	1.1	Anthracycline based

(port) and none of the patients had a central venous catheter. Only three (3.2%) of the patients had steroid use. None of the patients included in the study were followed up in the intensive care unit, blood was not transfused, and total parenteral nutrition was not given. CMV DNA PCR was not positive in any patient in the study.

The mean leukocyte and neutrophil counts of the patients before the chemotherapy were 7,856/mm3 and 5,109/mm3, respectively. The nadir of leukocytes was seen on 7th day of chemotherapy, with the mean leukocyte and neutrophil counts of 6,213/mm3 and 3,928/mm3. After chemotherapy, severe leukopenia (< 500 /mm3) was not detected in 5 out of 93 patients. After 14 days, leukocyte and neutrophil counts were comparable, with a slight increase in leukocytes and a

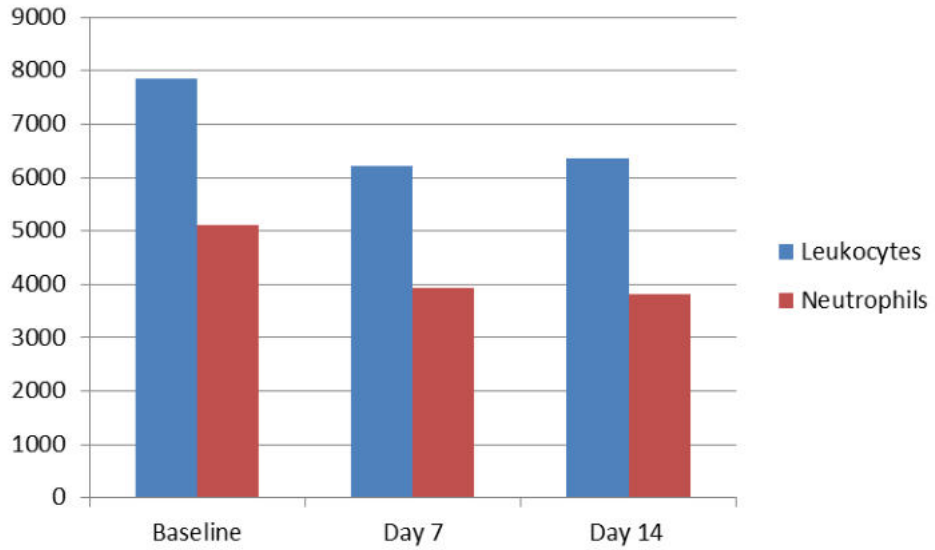

Fig. 1. Leukocyte and neutrophil count (/mm3) at baseline, 7th day and 14th day of chemotherapy.

Table 2. Cell counts of patients

Cells	Cell count (/mm^3, Mean ± SD)		
	Baseline	Day 7	Day 14
Leukocyte	7856 ± 2854	6213 ± 3336	6359 ± 3796
Neutrophils	5109 ± 2542	3928 ± 3022	3806 ± 3175
Neutrophils < 500/mm^3	0/93	5/93	0/93
Lymphocytes	1933 ± 846	1680 ± 750	1743 ± 844

SD = standard deviation

slight decrease in neutrophil counts (6,359/mm3 and 3,806/mm3, respectively) (Fig. 1, Table 2).

DISCUSSION

CMV reactivation can be life threatening in severity. Reactivation is seen as a result of immunosuppression which develops due to the decrease in lymphocytes and dysfunction of lymphocytes. Although this condition is seen mostly in transplant patients, chemotherapies used in patients with solid tumors also have reported to associate CMV reactivation [3, 5-8]. Our study is one of the few studies investigating CMV reactivation in solid tumor cases. CMV infection caused by reactivation causes fever, colitis, interstitial pneumonia, hepatitis, meningoencephalitis, radiculopathy in peripheral nerves, myelopathy, leucopenia or retinitis. This condition, which is also described as CMV syndrome, occurs in 60% of patients under the risk [6-10]. The mortality rate after infection with CMV reactivation is very high. In a study, CMV mortality was reported as 61.3% in patients with solid organ tumors. Mortality rates in these patients have been reported to be even higher than those with hematologic malignancies or who have undergone transplantation [9]. Emiroglu *et al*. [11] reported that CMV reactivation developed in a case of solid tumor with febrile neutropenia after chemotherapy. However, he was mortal after receiving CMV treatment after the seventh day. In CMV infection, mortality is reduced by accurate diagnosis and rapid treatment [7, 8, 12]. The mortality rate of infection caused by CMV reactivation in HIV patients, especially those receiving solid organ transplantation therapy, is high. This is especially important in countries where CMV seropositivity is close to 100%. Due to the immunosuppressive agents used in organ transplantation, aggressive use of immunosuppressives may cause reactivation of CMV [1, 2, 13]. When prophylaxis is not given after transplantation, it is reported that reactivation can occur in 25-30% of the patients within three months, and within six months with higher positivity [7, 8, 14]. CMV infection in HIV positive patients has also high morbidity or mortality, with association of low numbers of CD4 + T lymphocytes [2]. In HIV positive patients, infections such as retinitis, colitis, esophagitis and pneumonia due to CMV may develop. Studies have shown that CMV infection is common (between 59-100%) in HIV-infected patients [15]. This indicates that CMV reactivation will increase dramatically in cases lymphocytes cannot function or when number of lymphocytes decreases.

In our study, none of the patients with chemotherapy who were followed up with the diagnosis of solid tumor were found to have CMV reactivation. Studies evaluating CMV reactivation in patients with solid tumors are very rare. Some studies are available indicating that malignancy is not a risk factor in the development of CMV infection [16-18]. In addition, several studies showed that CMV reactivation might be due to the weakening of immunity [16]. In their study, Mera *et al*. [19]. found that CMV infection due to CMV reactivation was detected in 42% of patients with solid tumors in autopsy. In their large-scale literature review, Osawa and Singh [8] found that immunosuppression can cause CMV reactivation in 0-36% of inpatients in intensive care unit. Capria *et al*. [20]. reported that 35% of the patients with hematological malignancy had reactivation after chemotherapy with CMV infection. In a study con-

ducted by Kuo *et al*. [21] they reported that CMV infection due to reactivation was not detected in any patient with solid tumor who received chemotherapy. In other two studies, it was reported that CMV reactivation might be rare in patients with solid tumor diagnosed with chemotherapy [22, 23].

In light of the data provided, we may link the absence of CMV reactivation in our study for several reasons. As it is known, lymphocytes in the blood have an important role in preventing CMV infection. The decrease in the number of lymphocytes and mediators such as TNF and IL-1 may lead to CMV reactivation [21, 24-28]. Drugs used in chemotherapy of patients with solid tumors leads to immunosuppression and drugs reducing the number of lymphocytes in cancer patients may cause CMV reactivation [6, 21, 29]. Purine analogues, major chemotherapy drugs such as cyclosporine, high-dose steroids cause severe immunosuppression. This results in reactivation and increase in viral load in these patients [21]. None of our patients had severe neutropenia and lymphopenia. Taxane, platinum, 5-FU, gemcitabine and anthracycline-based drugs were used in patients included in our study and these drugs have the potential to cause neutropenia. However, none of these drugs have the ability to make significant lymphopenia. Based on these data another reason for the absence of CMV reactivation in our study may be the lack of chemotherapy drugs that cause severe immunosuppression. Although we have studied with a very large group, some solid tumor types might have an inadequate number of patients. However, we believe that our study may be a guide for future studies.

The change in the number of lymphocytes affects the rate of CMV reactivation. However, it is also stated that low lymphocytes do not always cause CMV reactivation. The reason for this is shown as the presence of an old immune response to CMV infection [17].

It has been reported that CMV infection due to reactivation may develop more in some solid tumor types than others [1, 25, 26]. CMV reactivation may be present in 5-75% of the hematology patients [10, 30]. In particular, CMV infection due to reactivation is reported to be higher in colon, lung and brain tumors compared to other solid tumors. CMV positivity was found in 90% of patients with these tumors [28]. In the study of Schlick *et al*. [6] two patients with pancreas cancer and one patient with breast cancer were reported to have CMV infection following chemotherapy. In our study, CMV reactivation was not observed although we had this group of patients.

Any situation that reduces the number of lymphocytes means that the most important defense mechanism against CMV is weakened. Steroids reduce the number of lymphocytes only with high doses for a long time [18]. The reason for the absence of CMV reactivation in three patients with steroid use in our study may be related to short-term and low-dose steroids disrupting cell function but not decreasing their number.

The CMV PCR test is a rapid and sensitive test that best detects the reactivation indicator in the detection of the virus [2] The immune response, which ELISA tests cannot detect, can be detected by PCR. In the study of Emiroglu *et al*. [11] PCR test detected CMV in a CMV-pp65A-negative patient with solid organ tumor. This shows that molecular detection of the virus is more sensitive and specific than immunological response-based ELISA method. This test also provides additional information as the amount of viral load will be determined by the PCR test [10, 25, 26].

CONCLUSION

CMV infection can be mortal especially in patients with immunosuppression. Prophylaxis in patients with transplantation, prolonged use of steroids and immunosuppression in patients with transplantation can prevent mortality. When CMV infection is detected in patients with chemotherapy who have hematological malignancies and solid tumors, CMV DNA detection by PCR should be performed and treatment should be given rapidly. We conclude that CMV reactivation is very rare in patients with solid organ tumors receiving chemotherapy suggests that standard prophylaxis is not required.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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