EJMI

DOI: 10.14744/ejmi.2021.39203
EJMI 2021;5(1):142–147

Research Article

Chemotherapy Agents Used in the COVID-19 Pandemic and Previous Years in Non-Small Cell Lung Cancer Patients and Their Effects on Periodic Mortality: A Single-Center Experience

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Abstract

Objectives: The objective of the study was to evaluate chemotherapy agents used in the coronavirus disease-19 (COVID-19) pandemic and previous years and compare mortality rates of non-small cell lung cancer (NSCLC) patients who were receiving anticancer therapy.

Methods: Patients were analyzed retrospectively in three different groups; the first group (December 1, 2017-May 31, 2018), the second group (December 1, 2018-May 31, 2019), and the pandemic period group (PPG) (December 1, 2019-May 31, 2020).

Results: A total of 608 NSCLC patients were evaluated, 183 in the first group, 206 in the second group, and 219 in the PPG. Palliative anticancer therapy rates were 85.2% in the first group, 87.7% in the second group, and 74.4% in the PPG ($p<0.001$), respectively. There was no statistically significant difference between the three groups in terms of the preferred treatment agents. Mortality rate was found to be 21.9% in the PPG, and it was not significantly different from the other groups ($p=0.959$). The type of anticancer treatment agents had no statistically significant effect on mortality. The COVID-19-positive mortality rate among all NSCLC patients was 1.8% (4/219) in the PPG.

Conclusion: COVID-19 pandemic did not significantly change mortality rates compared to previous years in this high-risk patient population.

Keywords: Anticancer therapy, chemotherapy, COVID-19, non-small cell lung cancer, mortality

Cite This Article: *Demirci A, Hacibekiroglu İ. Chemotherapy Agents Used in the COVID-19 Pandemic and Previous Years in Non-Small Cell Lung Cancer Patients and Their Effects on Periodic Mortality: A Single-Center Experience. EJMI 2021;5(1):142–147.*

Due to the coronavirus disease-19 (COVID-19) pandemic, peoples all over the world have been deeply affected by both physical health and psychological aspects.[1] After the announcement of the COVID-19 pandemic, immunosuppressed patients with cancer were declared high risk for severe disease.[2] Lung cancer patients were thought to be more at risk for COVID-19 due to the high rate of hospitalization and high mortality. Three Chinese studies showed that the most frequent type of cancer in COVID-19-infected cancer patients was lung cancer.[3-5] Furthermore, according to data from China, where the pandemic first started, Chinese Respiratory Oncology Collaboration recommended that non-small cell lung cancer (NSCLC) patients who need to be hospitalized for anticancer therapy should be excluded from COVID-19 infection.[6]

European Society of Medical Oncology identified that cancer patients may be at higher risk of severe illness from COVID-19 who having chemotherapy or have received

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Submitted Date: February 04, 2021 **Accepted Date:** March 02, 2021 **Available Online Date:** April 03, 2021

chemotherapy in the past 3 months.[7] In a retrospective, multicenter, cohort study, Yang et al.[8] described clinical characteristics and outcomes of patients with cancer and COVID-19. They analyzed the results of 205 patients with cancer and laboratory-confirmed COVID-19 infection. After breast and colorectal cancer, lung cancer was the third most common solid tumor type. Patients receiving chemotherapy within 4 weeks before symptom onset and male sex were risk factors for death during admission to hospital.[8] Similarly, there were other studies on the mortality of patients who were positive for COVID-19 during receiving anticancer treatment. Data are not available regarding the overall mortality compared to previous years for patients receiving anticancer therapy.

We aimed to evaluate the baseline characteristics and mortality rates NSCLC patients who were receiving anticancer therapy during the COVID-19 pandemic period in a tertiary hospital. Different from other studies, we compared mortality rates between December and May in 2017-2018, 2018-2019, and 2019-2020 (COVID-19 pandemic period).

Methods

This single-center study designed retrospectively. The files of all patients who were followed up and treated at our oncology clinic between December 1, 2017, and May 31, 2020, were scanned. A total of 608 NSCLC patients were evaluated. Data for the first 6 months of 2020 were compared with the first 6-month periods of the previous 2 years, as it reflects the first peak spread of the pandemic. Therefore, patients were analyzed in three different groups; the first group (December 1, 2017-May 31, 2018), the second group (December 1, 2018-May 31, 2019), and the pandemic period group (PPG) (December 1, 2019-May 31, 2020).

Only patients receiving chemotherapy and immunotherapy were selected and recorded. Patients' age, gender, presence of metastatic disease, type of chemotherapy, application purpose, and method of chemotherapy were recorded by examining patient files. Anticancer treatments were classified into two different groups in terms of risk of febrile neutropenia (>20% high risk and <20% moderate/low risk).[9]

Therapies consisting of single anticancer therapy and more than 1 drug were accepted as monotherapy and combination therapy, respectively. The death information and dates of the patients who died were obtained from the hospital records.

Inclusion criteria; patients with a diagnosis of NSCLC >18 years of age and patients who had been receiving chemotherapy or immunotherapy within the mentioned 3 time periods were included in the study and the patients who did not receive anticancer therapy or only those who had routine control were excluded from the study.

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Science-22 for Windows (SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms and probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. We performed analyses to describe and summarize the distributions of variables. Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as whole number and percentages. The means of normally distributed continuous variables such as age between three different time period groups were compared using the one-way ANOVA test. One-way ANOVA followed by Duncan's multiple comparison of the means revealed significant differences between the groups. The Chi-square test was used to compare the proportions in different groups. To determine the relationship between type of treatment and mortality, multivariate logistic regression was performed. The statistically significant two-tailed p-value was considered as <0.05.

Results

A total of 608 NSCLC patients were evaluated, 183 in the first group, 206 in the second group, and 219 in the PPG. No difference was found between the three different period groups in terms of mean age (p=0.189) and gender distribution (p=0.235). Palliative anticancer therapy rates were 85.2% in the first group, 87.7% in the second group, and 74.4% in the PPG (p<0.001), respectively. There was a statistically significant difference between groups and difference was due to the PPG (Table 1). Chemotherapy characteristics were also compared. When evaluated according to the risk of febrile neutropenia (≥20% and <20%), chemotherapy regimens were similar (p=0.416) in all three groups. Monotherapy was significantly less preferred in the second group (17.5%, p<0.001). There was no statistically significant difference between the three groups in terms of the preferred treatment agents. Most preferable anticancer therapy was platinum+taxane-based chemotherapy (Table 1).

Mortality rate was found to be 21.9% in the PPG, and it was not significantly different from the other groups (p=0.959) (Fig. 1). The distribution of mortality by months between three different periods was evaluated, there was no death in the first group in December, while the PPG had a lower mortality rate than the other groups in May (0.8% vs. 8.5% and 6.2%; PPG vs. first group and second group, respectively, p=0.009) (Fig. 2).

Table 1. Comparison of the baseline characteristics and the properties of anticancer therapy of the groups according to the periodic time interval

	Periodic time interval			
	First group	**Second group**	**Pandemic period group**	**p**
	(December 1, 2017-May 31, 2018) n=183	(December 1, 2018-May 31, 2019) n=206	(December 1, 2019-May 31, 2020) n=219	
Age, years	64.5±8.6	65.6±8.4	65.1±8.2	0.189
Gender, female/male, n (%)	18/165 (9.8/90.2)	26/180 (12.6/87.4)	34/185 (15.5/84.5)	0.235
Risk of febrile neutropenia, n (%)				
≥20%	-	-	1 (0.5)	0.416
<20%	183 (100)	201 (100)	218 (99.5)	
Monotherapy, n (%)	57 (31.1)	**36 (17.5)**	71 (32.4)	**<0.001***
Combination, n (%)	126 (68.9)	**170 (82.5)**	148 (67.6)	
Anticancer therapy, n (%)				
Palliative	156 (85.2)	183 (88.8)	**163 (74.4)**	**<0.001****
Non-palliative	27 (14.8)	23 (11.2)	**56 (25.6)**	
Treatment agents, n (%)				
Platinum+Taxane based	74 (40.4)	96 (46.6)	84 (38.4)	
Platinum based	64 (35)	74 (35.9)	68 (31.1)	
Taxane based	12 (6.6)	9 (4.4)	18 (8.2)	
Pemetrexed	9 (4.9)	4 (1.9)	15 (6.8)	0.078
Vinorelbine	8 (4.4)	9 (4.4)	9 (4.1)	
Gemcitabine	13 (7.1)	12 (5.8)	22 (10)	
Gemcitabine+vinorelbine	3 (1.6)	2 (1)	0	
Immunotherapy	0	0	3 (1.4)	

*The difference is due to the second group. **The difference is due to the pandemic period group.

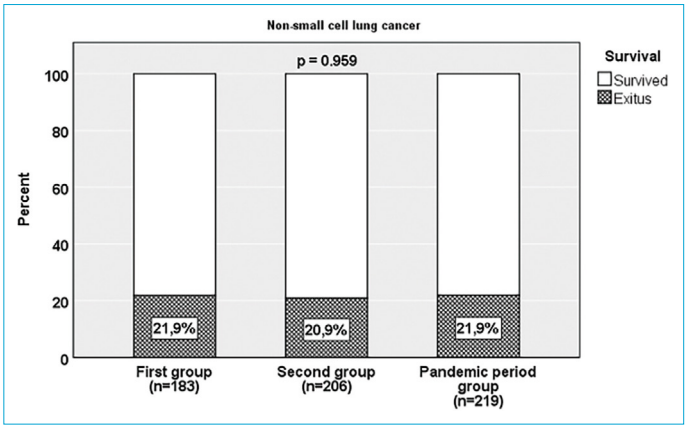

Figure 1. Comparison of the mortality rates of the first group (December 1, 2017-May 31, 2018), the second group (December 1, 2018-May 31, 2019), and pandemic period group (December 1, 2019-May 31, 2020) by years.

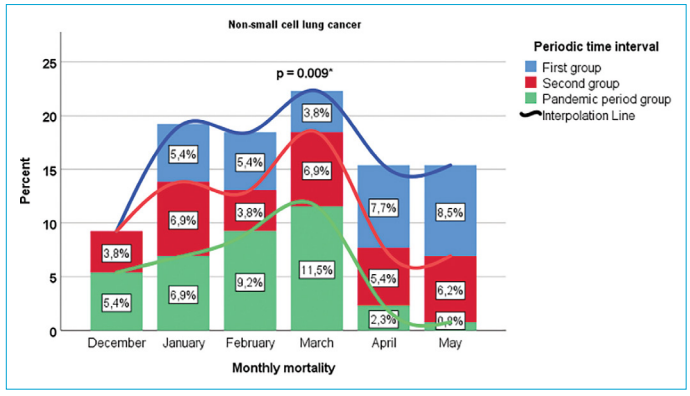

Figure 2. Comparison of monthly mortality rates in non-small cell lung cancer (NSCLC) patients. (*) The difference in monthly mortality in NSCLC patients is between December for the first group and December for the pandemic period group (PPG). In addition, mortality rate in May is significantly lower in the PPG than other groups.

Logistic regression analysis was performed separately in all three groups to determine whether anticancer treatment agents had an effect on mortality (Table 2) with no differences found by treatment agents.

COVID-19 positivity was detected in 7 (3.2%) patients by nasopharyngeal swab (tested by real-time polymerase chain reaction). The COVID-19-positive mortality rate among all NSCLC patients was 1.8% (4/219) in the PPG.

Discussion

In this study, we compared the cross-sectional mortality rates of patients with NSCLC ongoing anticancer therapy

Table 2. Logistic regression analysis of treatment agents on mortality

	OR	95%CI lower	95%CI upper	p
First group				
Treatment agents				
Platinum+Taxane based (ref.)				0.989
Platinum based	1.204	0.536	2.706	0.653
Taxane based	1.311	0.316	5.447	0.709
Pemetrexed	1.124	0.211	5.973	0.891
Vinorelbine	0.562	0.064	4.924	0.603
Gemcitabine	1.180	0.288	4.829	0.818
Gemcitabine+vinorelbine	1.967	0.167	23.169	0.591
Immunotherapy	0.287			
Second group				
Treatment agents				
Platinum+Taxane based (ref.)				0.643
Platinum based	0.887	0.414	1.900	0.757
Taxane based	0.475	0.056	4.023	0.495
Pemetrexed	0.000	0.000		0.999
Vinorelbine	1.900	0.436	8.270	0.392
Gemcitabine	2.714	0.779	9.463	0.117
Gemcitabine+vinorelbine	0.000	0.000		0.999
Immunotherapy				
Pandemic period group				
Treatment agents				
Platinum+Taxane based (ref.)				0.706
Platinum based	0.951	0.433	2.085	0.899
Taxane based	1.833	0.604	5.563	0.284
Pemetrexed	0.564	0.117	2.731	0.477
Vinorelbine	0.458	0.054	3.908	0.476
Gemcitabine	1.711	0.606	4.829	0.310
Gemcitabine+vinorelbine	0.000	0.000		0.999
Immunotherapy	0.015			0.999

OR: Odds ratio; CI: Confidence interval.

in 3 different years at same time periods. We did not find difference between three groups.

Considering that there may be cases that were not detected before March 10, 2020, when the first COVID-19 cases were seen in our country, we reviewed the medical records and deaths between December 2019 and May 2020. Initially, it was predicted that mortality rates may have increased, based on other studies showing that cancer patients, especially those with lung cancer, increased the severity of COVID-19.

We do not have sufficient data on COVID-19 disease severity and mortality in patients receiving active cancer treatment. In a study of Luo et al.,[10] 102 COVID-19-positive lung cancer patients were evaluated by the researchers of the Memorial Sloan Kettering Cancer Center (MSKCC) in New York. It was shown that the severity of COVID-19 was high in lung cancer patients with 62% of patients being hospitalized and 25% who died. Although severe, COVID-19 explained for a small number of overall lung cancer deaths in the MSKCC during the pandemic (11%). Similar to our study, median age was 68 years and 72% of patients had metastatic or active lung cancer. It was concluded that the operation or anticancer therapy due to lung cancer did not affect the severity of COVID-19. COVID-19 was associated with poor prognosis in patients with lung cancer, but this was due to patient-specific characteristics, not cancer-specific features.[10] In another retrospective study, Rogado et al.[11] investigated cumulative incidence of COVID-19 in lung cancer patients. Seventeen of the 1878 (0.9%) COVID-19 patients were lung cancer and most frequent pathologic subtype was NSCLC (n=16). While the number of patients who died was 192 (192/1878, 10%) in the total COVID-19-positive population,

9 of the 17 lung cancer patients died (52.3%) (p<0.0001). Mortality rate of lung cancer patients was higher than general population. The high mortality rate in lung cancer was attributed to the fact that most patients had active cancer or were receiving anticancer therapy.[11] The mortality rate of COVID-19-positive NSCLC in our patients was 57.1%, similarly, all of our patient groups consisted of patients who received anticancer treatment.

Rogado et al. reviewed 1069 cancer patients admitted to hospital between February 1, 2020, and April 7, 2020. They determined 4.2% COVID-19 diagnoses in cancer patients and 0.6% in total population (p<0.00001). In cancer patients, mortality rate was 42.2%, and in total population, mortality rate was 13.1% (p=0.0001).[12] In our study, seven patients were COVID-19 positive and four of them died, and the mortality rate for COVID-19-positive NSCLC was found to be 57.1%. We could not compare whether there was a change in the mortality of patients receiving chemotherapy in other centers compared to previous years, because there was no study in a similar design to our study.

In a study from Spain, Calles et al.[13] examined 23 lung cancer patients diagnosed with COVID-19. The case fatality rate was 35% (8/23). Although there were factors associated with mortality, tumor status, clinical baseline conditions, and inflammation markers, a statistically significant relationship was not found in a multivariate model. A total of 242 lung cancer patients receiving systemic therapy had the rate of incidence and mortality of COVID-19 was 4.5% and 2.1%, respectively. The incidence and mortality rate of COVID-19 did not change according to the type of anticancer treatment.[13] In our study, we did not carry out COVID-19 test all symptomatic patients. We were only able to obtain COVID-19 positivity information from hospital records. As such, the incidence of COVID-19 was 7/219 (3.2%) and the mortality rate was 4/219 (1.8%) in our patients receiving chemotherapy in PPG. There were no differences in mortality rate by type of cancer treatment. Our results were consistent with the results of the research conducted by Calles et al. In a study by Yu et al.[3] in China, they explained that patients with NSCLC had a higher incidence and severity of COVID-19. In a total of 1524 patients with cancer, 228 had NSCLC. The incidence of COVID-19 was 3.1% (7/228) in NSCLC patients. Two (28.6%) of the seven patients who were positive had died. In the study of Yu et al., COVID-19-positive mortality rate among all NSCLC patients was 0.8% (2/228). The reason for the higher incidence of mortality in our study may be that all of our patients were receiving anticancer treatment.

In a prospective cohort study, Lee et al.[14] compared cancer patients COVID-19-positive with a parallel non-COVID-19 United Kingdom cancer control population. They analyzed the impact of tumor subtype and patient demographics on prevalence and mortality from COVID-19. The all-cause case fatality rate in patients with cancer after COVID-19 infection was significantly associated with increasing age, older patients (80 years and older) had a higher risk. Patients with hematological malignancies who had recent chemotherapy had an increased risk of death with 2-fold during COVID-19-associated hospital admission. An increased case fatality rate was not observed in the COVID-19-positive lung cancer cohort compared to the remaining population with cancer. In the COVID-19-positive cohort, they concluded that patients with lung cancer were not a specifically susceptible group.[14]

There could be different reasons why the mortality rate did not increase in our patient population. First, there may be that terminal stage patients were not brought to the hospital by their relatives. Second, we may have preferred the best supportive care in NSCLC rather than chemotherapies after 2nd line therapy. Third, the mortality rate may not have increased due to the strict measures taken.

The potency of our study was that the characteristics of patients and properties of anticancer agents were similar to those of previous years. The major limitation of the study was, we could not exclude COVID-19 diagnosis in all died patients. Another limitation was that patients with active cancer who received oral anti-hormonal therapy and other oral targeted treatments did not be included. As a result of the precautions taken during the pandemic period, patients who received oral anticancer treatment were not included because the frequency of visits to the hospital decreased, they could obtain their reported medicines from pharmacies and their follow-up could continue with telemedicine.

Conclusion

We gave the mortality rate of patients with NSCLC receiving anticancer treatment during COVID-19 pandemic period and compared previous years. COVID-19 pandemic did not significantly change mortality rates compared to previous years in this high-risk patient population. Our study data included the winter-spring months of the year, however, data of mortality in summer and autumn seasons are needed.

Disclosures

Acknowledgment: We thank to the management of Sakarya University Training and Research Hospital.

Ethics Committee Approval: The study protocol was approved by Sakarya University Faculty of Medicine Ethics Comitee with 04/13/2020 and 16214662/050.01.04 number.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declare no potential conflict of interest.

Financial Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

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