Evaluatıon Of Sars-Cov-2 Infectıon In Cancer Patıents: Sıngle-Center Experıence From Turkey

Kanser Hastalarında Sars-Cov-2 Enfeksiyonun Değerlendirilmesi: Tek Merkez Deneyimi

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ÖZET(times new roman, 10 punkto, Ortalı,kalın, çizgiden bir boşlukla ayrılarak)

GİRİŞ ve AMAÇ: COVID-19 krizi sürecinde kanserli hastalarının bakımı ile ilgili önemli sorunlar bulunmaktadır. Bu hasta grubunun hem kanser tedavilerinin gecikmesi ile karşılaşılabilecek önemli mortalite riski hem de kemoterapi, radyoterapi, immünoterapi gibi antikanser tedavilerine bağlı gelişebilecek immünsüpresif durumları nedeniyle olası SARS-Cov-2 enfeksiyonu sırasında kötü prognoz ve mortalite riski bulunmaktadır. Bu nedenle pandemi dönemlerinde kanser hastalarının tedavilerinin devam etmesi ve enfeksiyon riskinin en aza indirilmesi için önemli tedbirler alınması gerekmektedir. Biz de tüm bu sorunlara cevap bulmak amacıyla hastanemiz acil servis, pandemi polikliniği, medikal onkoloji polikliniklerine COVID-19 bulguları ile başvurmuş solid malignite tanılı hastalarımızı retrospektif olarak taramayı amaçladık

YÖNTEM ve GEREÇLER: 11 Mart 2020 - 11 Mayıs 2020 tarihleri arasında Ankara Dr. A. Yurtaslan Onkoloji Eğitim ve Araştırma Hastanesi medikal onkoloji polikliniği, acil servis ve pandemi polikliniğine COVID-19 hastalığı semptom ve/veya bulguları ile başvuran ve daha önce solid organ malignitesi tanısı olan, tıbbı onkoloji kliniğimizde takipli 76 hasta retrospektif olarak incelendi.

BULGULAR: Başvuruda en sık görülen semptomlar;kuru öksürük (33, %43.4), ateş (23, % 30.3), yorgunluk (23, %30.3) ve dispne (23, %30.3) idi. Otuz dokuz vakaya (%51.3) COVID-19 rRT-PCR testi yapıldı.Dört hastanın (%5.2), COVID-19 rRT- PCR testi pozitif sonuçlandı.Bu sayı, aynı dönemde polikliniğimize başvuran yaklaşık altı bin kanser tanılı hastalarımızın % 0.06 'sını oluşturuyordu. rRT-PCR testi pozitif hastalar; evre 2 meme ca, 2. basamak kemoterapi alan mesane ca ve kemonaif evre 4 mide ca olup yoğun bakıma ünitesine yatışları gerekmedi ve iyileşmiş olarak taburcu oldukları öğrenildi

TARTIŞMA ve SONUÇ: Bulgularımız, mevcut pandemide kanser hastalarının daha kötü seyrini ve mortalitesini desteklememektedir. Bu durumun hastanemizin, onkoloji ağırlıklı hizmete devam edilmesi nedeniyle nisbeten korunaklı olup aktif covid hastasının takip edilmemesinin yanısıra çalışma sistemimizde yaptığımız önemli değişikliklerden dolayı (triyaj, polikliniklerde yer değişikliği yaparak sosyal mesafe korunması, maske takılması, remisyondaki kontrol hastaları, kemoterapi öncesi semptom sorgulama ve danışma için kullanılan teletıp uygulamaları gibi) kanser hastalarının hastaneye geliş sıklıklarını azaltarak, COVID-19 enfeksiyon riskini azalttığımızı düşünmekteyiz.

Anahtar Kelimeler: COVID-19, Kanser, Kemoterapi, Risk

ABSTRACT

INTRODUCTION: Oncologists from all over the world have important problems about the follow up and treatment of cancer patients during the COVID-19 crisis.Cancer patients have a poor risk of prognosis during SARS-Cov-2 infection due to both the significant risk of mortality that can be encountered with delayed cancer treatments and immunosuppressive conditions.We aimed to evaluate solid cancer patients with COVID-19 findings retrospectively to find an answer about the management of these patients during outbreak.

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METHODS: Between March 11,2020 and May 11,2020,76 patients who had solid organ malignancy were admitted to the Ankara Dr. A. Yurtaslan Oncology Training and Research Hospital with symptoms suggestive of COVID-19 infection were examined retrospectively.
RESULTS: The most common symptoms at admission were: dry cough, fever.COVID-19 RT-qPCR test was performed in 39 cases.The COVID-19 RT-qPCR test results were positive in four patients.This number constituted 0.06% of 6000 cancer-diagnosed patients admitted to our outpatient clinic.Among the patients who were positive for COVID-19 with RT-qPCR, one patient had stage2 breast carcinoma and was not actively receiving chemotherapy, another had newly-diagnosed stage 4 gastric carcinoma and was treatment-naïve, another was receiving radiotherapy and capecitabine for locally advanced rectal cancer, and the final patient had stage4 bladder cancer and was receiving second-line chemotherapy.Of these four patients, only one patient needed intensive care, while the other three recovered with intensive care-free medical treatment.
DISCUSSION AND CONCLUSION: Our findings do not support previous studies that have resulted in worse prognosis and mortality in cancer patients in the current pandemic.Our tertiary center based on oncology might provided the protection of COVID-19 infection due to non-followed COVID-19 positive patients.In addition, changes in our working system as; triage, displacement in polyclinics, communication by telemedicine with patients in remission, symptom questioning and consultation before chemotherapy, supply less frequency of routine hospital visits of cancer patients resulted reduced the risk of COVID-19 infection.
Keywords: Cancer, Chemotherapy, COVID-19, Risk

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the categorical diagnosis of the respiratory infection first reported among a group of individuals admitted with pneumonia in December 2019 in Wuhan, China (1-2). The infectious agent causing this pneumonia was determined to be a new coronavirus (initially named 2019 novel coronavirus). The virus was later termed as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) (3). The SARS-Cov-2 infection was defined as a pandemic by the World Health Organization on March 11, 2020. As of May 22, 2020, there were 5,245,672 confirmed cases worldwide. In addition, 2,116,322 patients had recovered, while 336,085 patients died due to the virus (case fatality rate was 6.41% at the time of writing). In Turkey, the first case was announced by the Ministry of Health on March 11, 2020. As of May 20, 2020, there were 154,500 confirmed cases, 116,111 recovered patients and 4276 deaths (case fatality rate was 2.77%).

Oncology patients represent a critical group of patients. They are especially vulnerable to COVID-19, but their diagnosis and treatment had to continue uninterruptedly. Cancer patients are more susceptible to the infection than individuals without cancer due to malignancy and systemic immunosuppressive conditions caused by anti-cancer treatments such as chemotherapy and/or surgery (4-7). Moreover, it has been reported that these patients are at greater risk of COVID-19, and their prognosis is poor (8). However, there is insufficient data on the frequency and prognosis of COVID-19 disease in cancer patients, with the exception of several studies mostly small case series. In a recent study from China that reported results of 18 cancer patients among 2007 cases of COVID-19, it was found that patients with cancer had a higher risk for severe clinical events when compared to patients without cancer (8). While COVID-19 mortality rate was estimated at 2.3% overall, the mortality rate in cancer patients was reported to be 5.6% (9).

There are important challenges concerning the care of patients with cancer during the COVID-19 pandemic. It is rather apparent that cancer patients have worse prognosis and higher mortality with COVID-19 in relation with the cancer itself and also treatments, such as chemotherapy, radiotherapy and immunotherapy, which cause immunosuppression. Therefore, careful measures must be taken to continue the treatment of cancer patients while minimizing the risk of infection. In this study, it was aimed to analyze solid cancer patients who were admitted to the emergency department, pandemic outpatient clinics or medical oncology clinics of a single Oncology Training and Research Hospital with symptoms suggestive of COVID-19 retrospectively.

MATERIAL and METHODS

Study design and participants

Between March 11, 2020 and May 11, 2020, 76 patients who had solid organ

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malignancy were admitted to the Ankara Dr. A. Yurtaslan Oncology Training and Research Hospital medical oncology outpatient clinics, emergency department and/or pandemic outpatient clinics with symptoms suggestive of COVID-19 infection were examined retrospectively.

March 11, 2020 was chosen on purpose because the first case was announced on March 11, 2020 in Turkey. In particular, patients who were admitted with complaints of fever, cough, dyspnea, and/or those who had a history to have a contact with a COVID-19 patient, were evaluated as a medium- or high-probability suspect case according to the recommendations of the Ministry of Health. The patients with symptoms suggestive of COVID-19 infection were taken nasal and/or pharyngeal swab specimens and SARS-CoV-2 RNA was tested by real-time reverse transcriptase polymerase chain reaction (RT-qPCR), in moderate and high clinical suspect cases high resolution computer tomography was performed. Retrospective medical data were obtained from the hospital records of the patients and included demographic features, comorbid diseases, performance scores, diagnostic informationes, forms associated with treatment, duration of treatment, SARS-CoV-2 PCR results, and treatment results after COVID-19 diagnosis.

A 24-hour pandemic clinic outside the hospital's main building was established on 17 March 2020. Patients suspected to have COVID-19 were immediately directed to the Radiotherapy ward or the intensive care unit of the Department of Internal Medicine which had been vacated for pandemic response. The patients were transferred to designated pandemic-response hospitals if their COVID-19 RT-qPCRtests were positive.

This study was approved by the Ankara Dr. A. Yurtaslan Oncology Local Clinical Study Board and Republic of Turkey Ministry of Health Scientific Research Platform (2020-05-07, T11_29_00).

Statistical analysis

Continuous variables were presented as mean ± SD (standard deviation) or median (IQR) (Interquartile Range) accordingly. Categorical variables were presented as number (n) and percentage (%) values. The Shapiro-Wilk test was used to test the normality of distribution of continuous data sets. The Kaplan-Meier method was used for the evaluation of event time data, to estimate median time and the corresponding 95% confidence intervals (CI). All statistical analyses were performed by the use of SPSS version 26.0. Any p value of <0.05 was accepted to demonstrate statistical significance.

RESULTS

Seventy-six patients with a prior diagnosis of cancer who had COVID-19 symptoms were evaluated retrospectively among approximately 6000 patients who were admitted tomedical oncology outpatient clinics in a period of 60 days.The demographic and clinical features of the patients are shown in Table 1.

Median age was 57 (19-86) years, 39 (51.3%) patients were male. Twenty-one patients (27.6%) were active smokers. Thirty-nine patients (51.3%) had various comorbidities, including diabetes mellitus (13.2%), hypertension (26.3%) and chronic obstructive pulmonary disease (6.6%). The most common types of cancer among the patients were: breast cancer (n=19, 25.0%), lung cancer (n=16, 21.1%), and head and neck cancers (n=9, 11.8%), respectively. Among these patients, 40 (52.6%) had stage 4 malignancy. There was a history of lung metastasis in 27 patients (35.5%), and mediastinal radiotherapy in 8 patients (10.5%). Thirty-four patients (44.7%) had received chemotherapy, 5 patients had received (6.6%) immunotherapy, and 14 patients (18.4%) had received targeted therapy in the past 14 days. Twenty-five patients (32.9%) had the use of G-CSF for primary or secondary prophylaxis after chemotherapy.

The most common symptoms at admission were: dry cough (n=33, 43.4%), fever (n=23, 30.3%). Computed tomography of the thorax was performed in 50 patients (65.7%), while COVID-19 RT-qPCRtest was performed in 39 patients (51.3%). The COVID-19 RT-qPCRtest results were positive in four patients (5.2%). Thorax computed tomography findings of 10 patients (13.2%) were consistent with viral pneumonia, but only one of these 10 patients had a positive COVID-19 RT-qPCRtest result. Among the patients who were positive for COVID-19 with RT-

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qPCR, one patient had stage 2 breast carcinoma and was not actively receiving chemotherapy, another had newly-diagnosed stage 4 gastric carcinoma and was treatment-naïve, another was receiving radiotherapy and capecitabine for locally advanced rectal cancer, and the final patient had stage 4 bladder cancer and was receiving second-line chemotherapy in the past 14 days. Allpatients were hospitalized and only gastric carcinoma patient was hospitalized in intensive care unit for ten days and received favipiravir, plaquenil and antibiotic treatment. One patient received oseltamivir, plaquenil, and antibiotics, and the remaining two received plaquenil and antibiotic therapy only. All patients were discharged in good health.

Table 1. Demographicandbaselineclinicalcharacteristics ofcancerpatientswithsuspectedCOVID-19

		Patients(n=76)	%
Median Age (range: mim-max)		57 (19-86)	
Male Gender		39	51,30
Tumor diagnosis			
	Breast Cancer	19	25,00
	Lung Cancer	16	21,10
	Head and Neck Cancer	9	11,80
	Others	32	42,10
TumorStage			
	Stage I/II/III	36	47,40
	Stage IV	40	52,60
	LungMetastasis	27	35,50
History of PriorTreatment			
	Chemotherapy (<14 days)	34	44,70
	Targetedtherapy (<14 days)	14	18,40
	Immunotherapy(<14 days)	5	6,60
	Radiotherapy to mediastinum	8	10,50
Co-morbidities			
	Diabetes Mellitus	10	13,20
	Hypertension	20	26,30
	Chronic obstructive pulmonary disease	5	6,60
	other	4	5,20
Symptoms and signs at on admission			
	Dry Cough	33	43,40
	Fever	23	30,30
	Fatique	23	30,30
	Dyspnea	23	30,30
rRT-PCR test positive		4	5,20
Ct findings with viral pneumonia		10	13,10

Among the 10 patients (13.1%) whoseRT-qPCRtests were negative but tomography findings were suggestive of SARS-CoV-2 infection, four had lung cancer, one had breast cancer, one had colorectal cancer, one had malignant melanoma, one had

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gastric carcinoma, one had soft tissue sarcoma, and one patient had urothelial carcinoma. Two of these patients were actively receiving chemotherapy and one patient was receiving immunotherapy. Two of the patients with negative RT-qPCRresult who had computed tomography findings compatible with viral pneumonia died.

DISCUSSION

This study is one of the few studies focusing on the frequency of COVID-19 in patients with cancer. In our hospital, only 4 patients out of approximately 6000 who were admitted to our outpatient clinics between 11 March 2020 and 11 May 2020 were found to be positive for COVID-19 via RT-qPCRtest. This number constituted 0.06% of 6000 cancer-diagnosed patients admitted to our outpatient clinic. In addition, it was 0.18% of 2181 patients who were admitted to the pandemic outpatient clinic.

The initial data regarding the incidence of COVID-19 in cancer patients comes from Wuhan, China. In a single-center, retrospective study conducted by Jing Yu et al., SARS-CoV-2 infection was detected in 0.79% (12 patients) of the 1524 cancer patients who were admitted to the Radiation and Medical Oncology Department from December 2019 to February 2020 (10). This percentage was higher than the cumulative incidence of all COVID-19 cases diagnosed during the same time period in Wuhan (0.37%, 41,152/11,081,000; data as of 17 February 2020) (10). In a nationwide analysis with data drawn from 575 hospitals in China, 18 out of 1590 COVID-19 cases (95% CI = 0.61-1.65) were found to have a history of cancer, and this frequency was higher than the incidence of cancer in the Chinese population (285.83 per 100.000 people, 0.29%, according to the 2015 Cancer Epidemiology Statistics) (8). On the other hand, when we focus on data from the west, it was determined that 320 (6%) of the 5700 patients hospitalized with COVID-19 in New York City had a history of cancer (11).

According to this retrospective data, we may attribute the low incidence of COVID-19 positive patients in Turkey to the early measures taken by the Ministry of Health throughout the country, in addition to further precautions taken by our center and Medical Oncology Clinics.Ankara Dr. A. Yurtaslan Oncology Training and Research Hospital is a huge center giving service mostly to oncology patients. During the triage of patients, body temperature measurements were performed at all hospital entrances, and disinfectants and surgical masks were provided for patients. Additionally, individuals accompanying patients were not accepted into waiting rooms, and strictly followed social distancing measures. We have also imposed restrictions for the visitors of patients in wards.

In order to reduce elective arrivals to the medical oncology outpatient clinics, patients in remission were called by telephone and their appointments were postponed. The entrance doors of the chemotherapy service and outpatient clinics were separated; thus, enabling less interaction of patients. Other precautions that could be taken to reduce risks in chemotherapy patients were discussed case by case and planned to be undertaken when necessary (such as switching from intravenous therapy to oral therapy or extending weekly treatments, or extending the duration of supportive treatments such as bisphosphonate / denosumab etc.).

One of the most important of these measures may be the use of telemedicine services which are utilized throughout world (12). Two separate phone lines were established for patients receiving chemotherapy and those with scheduled controls. Through these, patients were contacted and their control dates, laboratory investigations and results were organized remotely; thus reducing their frequency of hospital visits. In addition to counseling services through phone, we also called patients scheduled for chemotherapy before treatment dates for anticipatory triage and questioned their symptoms (fever, cough, shortness of breath). Patients with these symptoms were directed to appropriate clinics. However, as the administrative, legal and financial infrastructure of telemedicine regulations are developing in our country (similar to many countries), there were difficulties in practical application.

In our study, 76 patients were evaluated and 51.3% of the patients were male, median age was 57 years, and the most common type of cancer (25%) was breast cancer. The most common symptoms at admission were dry cough (n=33, 43.4%), fever (n=23, 30.3%) and dyspnea (n=23,

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30.3%). In a study evaluating 28 cancer patients with COVID-19 from three hospitals in Wuhan, China, 67% of the patients were male, median age was 65 years, and the most common type of cancer was lung cancer (7 patients, 25%) (13). In a nationwide analysis in China, the majority of 18 cancer patients diagnosed with COVID-19 had lung cancer (5 patients, 28%), and the mean age was 63.1 years (8). In a study evaluating five COVID-19 patients with cancer in Italy, the mean age was 71.64 ± 10.08 years (range 50 to 84 years), 80% of the patients were male (male / female 20/5), and the most common type of cancer was lung cancer (8 patients, 32%) (14).Although the data on the clinical features of cancer patients infected with SARS-CoV-2 are limited to the retrospective data drawn from small case groups; thus limiting their reliability, we also found that more than half of the patients in our study were male.

Only four of the approximately 6000 patients that applied to our outpatient clinic over the two-month period of this study were tested positive for SARS-CoV-2 via RT-qPCR. Of these four patients, only one patient needed intensive care, while the other three recovered with intensive care-free medical treatment.However, currently available retrospective studies show that the disease is more severe and mortal in the patients with malignancy. In a multicenter study conducted in Wuhan, China, 105 cancer patients diagnosed with COVID-19 and 536 patients without cancer were compared. Patients with cancer were found to have higher mortality rate [OR: 2.34; 95% CI (1.15-4.77); P = 0.03], higher ICU admission rate [OR: 2.84; % 95 CI (1.59-5.08); P <0.01], at least one severe or critical symptom rate [OR, 2.79; 95% Cl, (1.74-4.41); P <0.01], and increased likelihood for the need for invasive mechanical ventilation (15). In a study from Italy, comprised of 25 cancer patients infected with SARS-CoV-2 as of 18 March 2020, it was found that 9 (36%) patients died, and 16 (64%) patients recovered from pneumonia; whereas, in the control group, death percentage was 16.13%, while 83.87% recovered (14). In New York, 218 cancer patients that were positive for COVID-19 were examined between 18 March and 8 April 2020. The study reported that 61 (28%) cancer patients died, while case fatality rate was 37% (20/54) in hematological malignancies and 25% (41/164) in solid malignancies (16).

Our findings do not support previous studies in terms of findings that show worse prognosis and mortality among cancer patients in the current pandemic. This may be due to the difference in the intensity of the pandemic in our region, the rules set by authorities, and the changes we have made in our routine working system. Since the first case was announced in Turkey, we have taken important steps to ensure that we can continue functioning, while also reducing the risk of infection.

Our study has some limitations. First, this was a retrospective study. Tests were ordered based on the evaluation of risk according to symptoms and findings; thus, not all patients underwent testing. In addition, our results do not reflect correct prevalence in our entire patient population due to the utilization of curfews, and the fact that patients residing in other cities were applying to other centers for their follow-up studies.

As a result, we can reliably suggest that the treatment of cancer patients should be continued during the pandemic, albeit strict measures to prevent transmission of infections should be taken, and it must be noted that teamwork is essential for successful operation. Appropriate isolation protocols should be established when it is considered that recurrent hospital visits pose a potential risk for SARS-CoV-2 infection among cancer patients. Telemedicine strategies and the establishment of “clean hospitals” (centers that do not directly treat COVID-19 patients) are among the important measures to be taken.

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