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The impact of Coronavirus disease 2019 pandemic on the treatment of cancer patients: the first steps in this fight

*Gabriela Rahnea-Nita [1,2], Dumitru-Cristinel Badiu [3,4] *, Cristian Gabriel Popescu [3,4], Valentin-Titus Grigorean [3,4], Dragos Serban [3,5], Catalin Gabriel Smarandache [3,5], Roxana-Andreea Rahnea-Nita [1,2], Anda-Natalia Ciuhu [1], Mihaela Mandu [6], Liliana-Florina Andronache [7], Alexandru-Rares Stoian [3,4]*

Abstract

Background: The new Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents a global threat due to its increased mortality, especially among the elderly and people with severe comorbidities, such as cancer.

Objectives: Through the specific measures that have been imposed to reduce the risk of infection and death, the working hypothesis is prepared: Coronavirus disease 2019 (COVID-19) pandemic has drastically decreased the hospital admissions of cancer patients, the frequency of hospitalizations and determined an increased mortality rate through the infection with SARS-CoV-2 virus in cancer patients.

Methods: For a period of 16 weeks, the hospitalizations of patients to the Chronic Oncology-Palliative Care Department of "St. Luke" Hospital for Chronic Diseases, Bucharest, were analyzed, being compared to the same period of the previous year and, also, there were patients with symptoms specific to COVID-19 infection, tested for SARS-CoV-2 by means of RT-PCR.

Results: The data analysis shows a 53.7% decrease among hospitalized patients – with 51.4 for day hospitalization and 50.2% for inpatient hospitalization, during the COVID-19 pandemic. 4 patients out of the 477 admitted to the Oncology Department in this period had a positive RT-PCR SARS-CoV-2 test during their hospitalization and 5 patients with symptoms common for both cancer and COVID-19 had a negative result through specific testing (Table I, Table II). Two other patients recorded on the unit were infected with SARS-CoV-2 virus and required admission and treatment in the COVID-19 Department. The willingness of the cancer patient to consult a physician for admission has greatly decreased in the first 16 weeks from the declaration of the COVID-19 pandemic.

Conclusion: Cancer patients, although at an increased risk of being infected, did not exhibit severe symptoms, and the evolution of the symptoms and the performance state after the discharge from the COVID-19 department was influenced by the age and the associated comorbidities.

[1] Department of Oncology, "St. Luke" Hospital for Chronic Diseases – Palliative Care, postal code 810249 Bucharest, Romania

[2] Department of Oncology, Radiology and Hematology,"Carol Davila" University of Medicine and Pharmacy, postal code 020021 Bucharest, Romania

[3] Department of Surgery,"Carol Davila" University of Medicine and Pharmacy, postal code 020021 Bucharest, Romania

[4] Department of Surgery, "Bagdasar Arseni" Emergency Hospital, postal code 041915 Bucharest, Romania

[5] Department of Surgery, The University and Emergency Hospital, postal code 917151 Bucharest, Romania

[6] Department of Neuro-rehabilitation, "Bagdasar Arseni" Emergency Hospital, postal code 041915 Bucharest, Romania

[7] Department of Modern Languages,"Carol Davila" University of Medicine and Pharmacy, postal code 020021 Bucharest, Romania

E-mail corresponding author: doctorcristianbadiu@yahoo.com

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1. Introduction

In March 2020, when the COVID–19 was declared a pandemic, affecting the population of more than 110 countries on various continents, the published studies highlighted an increased mortality in elderly patients, with associated comorbidities, including cancer patients (Docea et al., 2020; Singh et al., 2020; Zhao et al., 2020).

It is argued that the current pandemic disturbed the international balance of physical and mental health since that the treatments followed before the lockdown had to stop or undergo a drastic change in the therapeutic setting (Archer et al., 2020; Boldrini et al., 2020; Conversano & Di Giuseppe, 2021; Di Giuseppe et al., 2021; Frisone, 2019; Gugliandolo et al., 2020: Humer et al., 2020; Merlo et al., 2020, 2021b; Orrù et al., 2020; Prout et al., 2020; Plakun, 2020; Swartz, 2020; Settineri et al., 2019a). Not being well-prepared to manage a state of emergency has contributed to the aggravation of stressful situations in the health field, especially when the progress of medicine and research has not yet been sufficiently tested to handle the effect of a pandemic although supported by a state of technological advancement (AIRyalat et al., 2019; Bernacki et al., 2016; Fontaine et al., 2009; Frisone & Micali, 2020; Gusenbauer & Haddaway, 2020; Millar et al., 2020; Schellekens & van der Lee, 2020). Considering the growing recognized role of psychological figures in the field of physical conditions (Martino et al., 2021; Merlo, 2019; Vicario et al., 2020, 2021; Vita et al., 2020), psycho oncological studies demonstrated the weight of the current pandemics on the patients' general and specific conditions (Ciążyńska et al., 2020; Espinel & Shultz, 2020; Klaassen & Wallis, 2021; Schade et al., 2020; van der Lee & Schellekens, 2020).

COVID-19 pandemic has a deep impact on the social and economic life worldwide, and is considered the most severe sanitary crisis since the Spanish flu, a hundred years ago. The first estimates of the death rate among the patients infected with SARS-CoV-2 in China were of 8%

for the age group 70-79 years, with an increase of up to 15% in patients aged above 80 years. Further studies estimated a fatality rate of 0.5-1% of the total number of infected people and 5% of those diagnosed (Dascalu et al., 2020; Serban et al., 2020). Moreover, a death rate of 11% was reported in patients with cardiovascular diseases, 7% in patients with diabetes and 6% in patients with chronic pulmonary diseases or neoplasms (Zhang et al., 2020a). The studies in China published until that date indicated an increased risk of severe respiratory symptoms and death in cancer patients who had undergone chemotherapy in the past 4 weeks (Tsamakis et al., 2020). Professional oncology associations have established recommendations to limit the risk of infection with SARS-CoV-2 in cancer patients, such as: reducing the number of hospitalizations, increasing the preference for oral chemotherapy in cases where intravenous chemotherapy can be replaced, increasing the interval of treatment administration, postponing patients in "follow-up" (Hanna et al., 2020; Rahnea-Nițǎ et al., 2020).

Thus, the oncology departments, but not only (i.e. diabetes departments) required a reorganization of the activity, taking into account the "risk-benefit" ratio and the recommendations for social distancing, reducing the contact period between the patients or the patient and the medical team, using specific protection equipment, the rigorous preservation of the disinfection measures (Mazilu et al., 2019a; Stoian et al., 2020a, 2020c; Zhang et al., 2020b). Moreover, problems occurring due to COVID-19 pandemic disregard the issues usually expected in classical treatment pathways, as in the case of psychopathological issues and the onset of mental disorders, which in the latter period seem to have increased, especially when compared to previous years (Di Giuseppe et al., 2018, 2020; Frisone et al., 2020a, 2020b, 2021; Lenzo et al., 2021; Merlo et al., 2021; Myles & Merlo, 2021; Sicari et al., 2021).

A significant importance in decreasing the risk of spreading the infection with SARS-CoV-2in medical facilities has proven to be the rigorous screening of these patients upon admission to the hospital, and respectively, of the medical staff, through the epidemiologic investigation (travels in the past 14 days, specific symptoms that have recently appeared, close contact with a person known to be infected with COVID-19) and RT/PCR SARS-CoV-2 testing (Zhang et al., 2020a).

On the other hand, the cancer patient with active disease, including metastasis or who undergoes adjuvant chemotherapy or radiotherapy is urgently required to continue his treatment in order to control the disease and the symptoms, thus increasing survival or cure chances (Bacinschi et al., 2020; Ciuhu et al., 2017; Mazilu et al., 2019b; Rodica Maricela et al., 2009). In some situations, the delay in beginning radiotherapy or chemotherapy is associated with the worsening of the

prognosis of the disease and the outcome, thus, the delay in beginning radiotherapy in patients with head and neck cancer increases the death rate by 16% for each month of delay; the delay in beginning chemotherapy in colon and anal cancer is also associated with the decrease of the survival rate. Moreover, terminally-ill cancer patients need specialized medical care to control the symptoms, especially pain, moderate/severe dyspnea, mediastinal compression syndrome, psychotic syndromes (Catrinoiu et al., 2020; Ciuhu et al., 2016, 2017a, 2017b; Papachristou et al., 2020; Rahnea-Nita et al., 2019; Schrag et al., 2020).

No health care system has been fully prepared to deal with the pandemic, and cancer patients, in turn, have been deeply affected by this new reality (Dimitriu et al., 2020; Mazilu et al., 2013). Currently, the immunization of the population by vaccination is considered a global priority, but research is needed for more data on the vaccination of cancer patients, being a special group of patients (Lee et al., 2020a).

The analysis of cancer patients who have benefited from specific treatment in the Chronic Oncology-Palliative Care Department of "St. Luke" Hospital for Chronic Diseases, Bucharest, for a period of 4 months from the declaration of the pandemic would highlight a significant decrease in the number of hospitalizations, compared to the same period of the year 2019, cancer patients with SARS-CoV-2infection would have moderate/severe symptoms and high mortality.

2. Methods

2.1 Participants

This was a retrospective, observational study in which, we evaluated the medical records of all the patients hospitalized (day hospitalization and inpatient hospitalization) in the Chronic Oncology-Palliative Care Department of "St. Luke" Hospital for Chronic Diseases, Bucharest, for a period of 16 weeks (the emergency state - March 15th-May 14th, 2020 and, the alert state, period- May 15th-July 09th, 2020).

All patients involved in the study signed an informed consent.

The approval of the Ethics Committee of "St. Luke" Hospital for Chronic Diseases, N.O. 6251/20.04.2020, was obtained.

Descriptive statistics were calculated using SPSS Statistics.

2.2 Measures

Starting from 15 March 2020, the Chronic Oncology-Palliative Care Department continued the daily activity regularly, the protocol of management of cancer patients allowing the continuation of treatment.

Patients were admitted in the unit for anticancer treatment (chemotherapies, targeted therapies and immunotherapies) and for palliative care.

The patients' preferences were also important in making the decision regarding the admission and the treatment.

Questionnaires asking for "flu-like" symptoms were performed by patients. Body temperature was also measured and patients were asked to wear masks.

Starting April 25th, the testing for SARS-Cov2 was performed, by means of the RT-PCR method, in all asymptomatic/symptomatic cancer patients admitted to the unit, according to the recommendations issued by the National Institute of Public Health Care (INSP) (prioritizing testing).

2.3 Procedure

We have analyzed all hospitalized cancer patients with symptoms common to both cancer and acute SARS-CoV-2 infection – cough, dyspnea, fever, chills and patients diagnosed with COVID-19 – symptoms, evolution, treatment.

2.4 Statistical analysis

Descriptive statistics were calculated using SPSS Statistics.

3.Results

During the period of 16 weeks of the COVID-19 pandemic, 477 patients were admitted to the Chronic Oncology – Palliative Care Department of "St. Luke" Hospital for Chronic Diseases, (52% -227/477 - patients with day hospitalization and 48% - 250/477 - patients with inpatient hospitalization), who had a number of 1,075 hospitalizations, with the following distribution, according to the hospitalization type: 54% - 585/1075 admissions with day hospitalization and 46% - 490/1075 admissions with inpatient hospitalization (some patients presented consecutive hospitalizations in order to respect the suggested frequency of the oncological treatment). The addressability for hospitalization favored the age group 50 to 79 years (85.6% - 408/477), as follows: 40.7 % (194/477) of the patients aged between 60-69 years, 23.9% (114/477) aged between 70-79 years and 21.0% (100/477) between 50-59 years and40.7% of the patients were

men and 37% were women. Out of the 447 patients treated during this period in the oncology department, 49.5 (236/477) had bronchopulmonary cancer, 14.3% (68/477) had colorectal cancer and 8.8% (42/477) had breast cancer.

During the similar period of last year (March 15th – July 9th, 2019), 969 patients were treated in the Chronic Oncology – Palliative Care Department of "St. Luke" Hospital for Chronic Diseases (467 with day hospitalization and 503 with inpatient hospitalization), with a number of 1,880 hospitalizations (884 with day hospitalization and 996 with inpatient hospitalization). Thus, the data analysis reveals a decrease by 53.7% of the hospitalized patients – with 51.4%-day hospitalization and 50.2% inpatient hospitalization, during the COVID-19 pandemic.

Moreover, there was a significant decrease in the number of cancer patients, in the main locations, as follows: (years 2019/2020) – bronchopulmonary cancer: 440/236; breast cancer: 85/42), but also an increase of the colorectal patients under treatment: 56/68 (years 2019-2020).

As for the year 2019, a relative frequency of 48.2% (= 467/969) of the patients with day hospitalization could be noticed in the total number of hospitalized patients, and as for the year 2020, this frequency is 47.6%. The two frequencies are close, so that we can state that the ratio of the patients admitted on an outpatient basis stays constant ($p = .829$ given the hi square test).

At the level of the year 2019, the relative frequency of "day" hospitalizations was 47.0% (= 884/1,880), and at the level of the year 2020 this frequency increases to 54.4%. The ratio of "day" hospitalizations significantly increases ($p < .001$ given by the Z test of ratios).

The diagnostic testing RT-PCR Sars-Cov2 was performed on patients who exhibited characteristic symptoms until April 25th when the testing was generalized to all asymptomatic/symptomatic cancer patients, on admission or 48 hours before the administration of the specific treatment, according to the recommendations issued by the National Institute of Public Health Care (INSP) for make testing a priority.

Between April 25th-June 9th, 325 patients were tested and 520 tests were run on the Oncology – Palliative Care Unit. A number of 4 patients were diagnosed with SARS-CoV-2 infection during this period, out of which 3 patients with day hospitalization and one with inpatient hospitalization on the unit. Also, during the same period, 2 other patients who were recorded and treated in our unit were diagnosed with COVID-19 infection in other medical facilities. According to the protocol, patients with active infection were transferred to other specialized departments and discharged after at least 2 negative consecutive RT/PCT tests. Thus, only 1.23% of the patients were diagnosed with COVID-19. On the other hand, between March 15th-April 24th, when testing was only performed on symptomatic patients, 5 patients were no longer

suspected of being infected with SARS-CoV-2 infection, which was refuted by the RT/PCR test. The main criterion for testing patients for SARS-CoV-2 by means of RT/PCR was the fever syndrome (fever>39 degrees Celsius). Out of the patients for whom the infection with COVID-19 was refuted, 3 of them had metastatic bronchopulmonary neoplasm. Out of them, 2 patients presented prolonged fever syndrome associated with severe secondary anemia, asthenia, increased serum transaminase values.

The evolution of the disease, prior to hospitalization and subsequent to testing, included the fever syndrome in a paraneoplastic syndrome with neoplastic disease in clinical and imaging evolution. The remission of the fever syndrome was obtained after changing the chemotherapy regimen. Two other patients presented fever syndrome during hospitalization and the result of RT/PCR SARS-CoV-2 test and the lung X-ray refuted the COVID-19 infection, their evolution was favorable under antibiotic therapy and antipyretics. Another patient who presented fever syndrome at home, after 7 days of chemotherapy and a negative RT-PCR SARS-CoV-2 test and a CT imaging examination 4 days before the occurrence of the symptoms, had a favorable evolution under corticotherapy, antibiotic therapy and antipyretics, most likely a post-chemotherapy fever syndrome being taken into account.

Of the 6 patients recorded on the unit and confirmed with SARS-CoV-2 infection by means of RT-PCR and subsequently with different degrees of interstitial pneumonia by assessment thoracic CT, 5 patients presented mild/moderate symptoms and one patient was asymptomatic. Prior to the diagnosis of COVID-19 infection, three patients had moderate dyspnea, two patients known with pulmonary neoplasm and one patient with breast cancer and associated pulmonary pathology (COPD pulmonary bronchiectasis). Respiratory symptoms were initially included among the symptoms of the already-known diseases. The admission of the patients with RT-PCR test for positive SARS-CoV-2 to a specialized department for the treatment of COVID-19 infection was mandatory. The hospitalization period ranged from 14 to 31 days. The 5 patients whose record we have kept after the discharge from the COVID-19 department, underwent treatment with drugs to relieve the symptoms and anticoagulants, 2 patients also requiring the association with Plaquenil in their treatment (due to the severity of the disease), 4 patients also underwent antibiotic treatment. After the discharge of the patients and in the clinical follow-up period of 2 months, 2 patients did not present remaining symptoms characteristic to COVID-19 infection, one patient maintained a minimum degree of dyspnea, most likely characteristic to neoplastic pulmonary disease, 2 patients presented clinical aggravation, either through severe dyspnea and increased need of oxygen therapy at home, or through marked asthenia and significant deterioration of the performance status.

4.Discussion

The significant decrease of hospitalizations in this period is explained by: the patients' decision to undergo symptomatic treatment at home in order to avoid the risk of infection, the postponement of the patients under monitoring or their referral to the outpatient services, the obligation of maintaining the distance between patients during hospitalization (isolation in the ward until receiving the result of the RT-PCR SARS-CoV-2 test) and limiting prolonged patient-patient contact.

The most frequent symptoms which indicate the suspicion of COVID-19 infection are fever (90-98%), cough (59-76%) and physical asthenia (30-70%) (Zhang et al., 2020a, 2020b), symptoms frequently seen in cancer patients as well, especially in pulmonary cancer patients or in patients with pulmonary metastasis. Cancer patients under active treatment – radiotherapy or chemotherapy and even supportive treatment, can present bacterial and viral pneumonitides with imaging characteristics similar to COVID-19 infection (Ciuhu et al., 2016). RT-PCR testing for SARS-CoV-2 makes the differential diagnosis hard in these situations (Zhang et al., 2020a).Under these conditions, to decrease the risk of spreading the SARS-CoV-2 infection, throughout hospitalization, the patients with symptoms suspicious of COVID-19 infection (especially – fever syndrome and acute respiratory distress) were referred to the emergency departments until the refutation of acute COVID-19 infection, only the cases that required the continuation of hospitalization for the control of the symptoms were subsequently hospitalized.

The decrease of the number of pulmonary cancer patients or of patients with cancer in other sites and the increase of colorectal cancer patients who consult physicians, in the two periods of time analyzed, i.e. such dynamics is mainly explained through several phenomena. During the emergency state, the general recommendations were to ensure the treatment of the patients with medical emergencies, affecting the compliance (Settineri et al., 2019b) related to the treatment of all other patients. Under these conditions, the patients presented to the emergency departments (ER) with severe symptoms, and the diagnosis of the disease was made when the optimal therapeutic moment had been exceeded.

In this situation, an exception is colorectal cancer, the disease for which patients went to the ER for symptoms of intestinal occlusion or sub-occlusion, and the diagnosis was made by surgery and the patient was subsequently referred to the oncology department. On the other hand, the transformation of the medical facilities into facilities that treat exclusively patients infected with SARS-CoV-2 virus, limited the patients' access to diagnostic investigations, such

as: bronchoscopy, upper digestive endoscopy, colonoscopy, imaging tomography, and as a consequence, the number of patients diagnosed with cancer has decreased.

Moreover, our department also deals with patients under palliative care or terminally-ill patients (Ciuhu et al., 2017a). Our observations were that these patients preferred home care by establishing the therapeutic schedule on the phone or by means of telemedicine-type consultations, due to the patients' fears or the fears of the patients' families to get infected or due to the families' wish to be as close as possible to the patient in the last days in the patients' lives (Catrinoiu et al., 2020; Ciuhu et al., 2016; Rahnea-Nita et al., 2019; Schrag et al., 2020).

The studies undergone so far highlighted a possible nosocomial transmission of COVID-19 infection. Considering the implications of clinical psychology that detect the incidence of fears and phobias in the individual's state of mental well-being (Friedrikson et al., 1996; Makarov, 2020; Öhman & Mineka, 2001; Settineri et al., 2019c; Strickland et al., 1997), this data could cause different risks concerning future hospitalization experiences.

A study performed on 138 patients revealed that 41.3% have contracted the infection throughout hospitalization, another study in Wuhan, China reported a nosocomial infection rate of 28.6 % in 28 cancer patients diagnosed with COVID-19 (Catrinoiu et al., 2020; Papachristou et al., 2020; Zhang et al., 2020b). Out of the 4 patients diagnosed with SARS-CoV-2 infection throughout the assessed 16 week-period, only one patient presented a positive result in RT-PCR testing, after 7 days from hospitalization in our unit. A nosocomial transmission is not clearly established in this situation, given the fact that throughout hospitalization, the patient's symptoms have significantly improved and a clear direct contact of the patient with an infected person could not be proven. The other 3 patients were diagnosed from the first day of hospitalization, either in day or in continuous hospitalization.

In the same study performed on 28 cancer patients with COVID-19 infection, 53.6% of the patients presented severe symptoms, with a death rate of 28.6% (Zhang et al., 2020b). Another study performed on cancer patients with SARS-CoV-2 infection revealed an onset period of the respiratory symptoms after 5-8 days from the contact with the infected person, with an average period of hospitalization of 7-10 days and 26% of the patients required admission to intensive care units (Catrinoiu et al., 2020; Dimitriu et al., 2020; Papachristou et al., 2020; Rahnea-Nita et al., 2019; Schrag et al., 2020). From our data, the 3 patients with dyspnea recorded as chronic pathology (pulmonary cancer and chronic obstructive bronchitis) presented a minimal aggravation of the respiratory symptoms in the week prior to the diagnosis of COVID-19 infection, none of the 6 patients recorded in our unit was admitted to "intensive care" - like

units, but the hospitalization period was much longer than the average mentioned in the previous study. None of the patient's required antiviral treatment and only 2 of the patients underwent treatment with Plaquenil according to specific protocols (Calina et al., 2020; Docea et al., 2020).

Although cancer patients on immunosuppressive ground (either through disease or through the specific treatments undergone) are considered to be at an increased risk of presenting severe symptoms or death due to SARS-CoV-2 infection. There are also studies that revealed that COVID-19 mortality in cancer patients is influenced by the advanced aged and comorbidities that are not related to cancer, while surgery and chemotherapy do not increase the COVID-19 mortality risk (but other future studies, performed on a larger number of patients will allow the confirmation or the refutation of the results) (Lee et al., 2020b; Stoian et al., 2020a, 2020b, 2021; Wang et al., 2020; Zugravu et al., 2012). None of our patients, all of them with stage IV of the disease, presented an increased risk of death throughout hospitalization and the treatment for COVID-19 infection, 3 of them undergoing specific treatment in the past 21 days (chemotherapy or immunotherapy).

5. Conclusions

The patients diagnosed with cancer are at an increased risk of infection with Sars-Cov-2, but the symptoms of COVID-10 infection are common to neoplastic symptoms, especially in pulmonary cancer patients or in patients with secondary pulmonary determinations, and the differential diagnosis is made by RT-PCR testing and thoracic CT. The evolution after COVID-19 infection may mark the worsening of the pre-existing symptoms, especially in the elderly, with minimal physiological recovery resources.

COVID-19 pandemic determined the restructuring of the activity in the oncology and palliative care units, which led to the decrease of the number of patients who benefited from the specific treatment, either chemotherapy or symptomatic treatment, during hospitalization.

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Authors' contributions

G R-N analyzed and interpreted the data, DS provided and cared for study patients, DCB took primary responsibility for communication with the Journal throughout the manuscript submission, peer review, and the publication process, A-N C collected and analyzed the data,

R-A R-N provided and cared for study patients, C G S collected the data, V T G served as a scientific advisor, L-FA linguistically revised the manuscript, M M revised the manuscript accordingly the Journal's recommendations for the authors, C G P prepared the literature review, A M D critically reviewed the study proposal, A-R S approved the final version for publication. All authors have read and approved the final manuscript.

Ethics approval and the consent to participate

We have prepared this manuscript with the approval of the Ethics Committee of "St. Luke" Hospital for Chronic Diseases, N.O. 6251/20.04.2020 having the patients' consent to participate.

Patient consent for publication

We have received the consent of the patients to participate in the study and to publish the article including data concerning them.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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