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Title

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Permalink

<https://escholarship.org/uc/item/05c8s584>

Journal

Mediterranean Journal of Emergency Medicine & Acute Care, 2(1)

ISSN

2642-7168

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Publication Date

2020

DOI

[https://doi.org/10.52544/2642-7184\(2\)1004](https://doi.org/10.52544/2642-7184(2)1004)

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Outpatient Management of Cancer Patients During the COVID-19 Pandemic: A Review and a Perspective from a Tertiary Care Center in the Middle East

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China. In no time, SARS-CoV-2 found its way to the whole world, to be declared as a pandemic by the World Health Organization (WHO) on March 11th, 2020. As this disease continues to take its toll on the world, we, at the American University of Beirut Medical Center, believe that it is essential to protect those who are at a particularly high-risk for contracting the virus, namely cancer patients. Besides complying with all the protective measures recommended by WHO, we developed quality improvement plans for the outpatient management of febrile neutropenia, pneumonia, and pulmonary embolism in cancer patients. The aim of such plans is to offer adequate management for cancer patients on an outpatient basis, whenever possible, and thus limit their admission rates together with their risk of contracting the novel virus, SARS-CoV-2.

Keywords: cancer, coronavirus, COVID-19, outpatient management

INTRODUCTION

In 2019, China declared the emergence of the novel, highly contagious Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Coronavirus disease 2019 (COVID-19) was first identified in Wuhan, a city in the Hubei Province of China. In no time, SARS-CoV-2 found its way to the whole world, to be declared as a pandemic by the World Health Organization (WHO) on March 11th, 2020.¹

Progressively, the health bodies assimilated the enormous repercussions of this infection. The consequences of COVID-19 impinged on the whole world's social, economic, and, undoubtedly, medical sectors.²

In light of the rapid spread of SARS-CoV-2 and the concomitant lack of approved effective pharmacologic agents,³ it became rather life-saving to adopt the protective measures advised by WHO, including social distancing and adequate hygiene precautions.^{4,5}

As this disease continues to take its toll on the world, we, at the American University of Beirut Medical Center (AUBMC), believe that it is of utmost importance to protect the most vulnerable, and in particular cancer patients. Providing adequate medical care for cancer patients during this crisis is highly demanding in view of the morbidity and mortality risks from cancer itself, as well as the added risk from contracting the virus.^{6,7} In Lebanon, the insufficient medical supply of personal protective equipment for the front-liners, together with the restricted capability of hospitals, amplified the challenges imposed by this pandemic.⁸ This was particularly evident in emergency departments (EDs) and intensive care units (ICUs) (with a total of 2026 ICU beds only).

Cancer patients frequently present to the ED due to the disease and disease progression symptomatology, as well as treatment complications.⁹ Given their increased risk for morbidity and mortality, largely

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attributed to their immunosuppression and disease progression, it is crucial that we offer them rapid yet focused care and safely discharge them from the ED, while ensuring the continuity of care on an outpatient basis. Such an initiative is based on the evidence that morbidity and mortality rates from COVID-19 are much higher in cancer patients compared to their counterparts who are cancer-free.¹⁰⁻¹²

At AUBMC, we made sure to comply with all the protective measures recommended by WHO. Besides, we established a pandemic evaluation clinic for suspected and confirmed cases of COVID-19 and narrowed down visiting hours and the number of allowed visitors. Perhaps, our best initiative was launching Telehealth for patients to receive healthcare from their homes by scheduling an online appointment with their primary care physician or specialist. Above all, we developed quality improvement plans for cancer patients, who are at a particularly high-risk for contracting the virus. The aim of those management plans is to offer adequate management for cancer patients on an outpatient basis, whenever possible, and thus limit their admission rates together with their risk of contracting SARS-CoV-2.

At our institution, we found that febrile neutropenia, pneumonia, and pulmonary embolism are the most common causes of presentation. Consequently, we specified, based on well-studied criteria and extensive literature review, cancer patients eligible for outpatient management. The aim of this approach was to reduce the number of hospital admissions, the load on the often-overstrained EDs, the financial burdens, the risk of hospital-acquired infections, and most importantly, to improve the quality of life (QoL) of these patients.

FEBRILE NEUTROPENIA

Febrile neutropenia (FN) refers to fever during an episode of neutropenia, particularly after a cycle of chemotherapy.¹³ It is defined as a single oral reading higher than 38.3°C, or a persistent oral temperature of at least 38.0°C over one hour and an absolute neutrophilic count (ANC) less than 500 cells/mm³ or expected to decrease below 500 cells/mm³ over the next 48 hours, following cytotoxic chemotherapy.¹⁴⁻¹⁶

Febrile neutropenia is one of the most concerning complications of cancer and/ or the use of aggressive chemotherapeutic regimens.^{17,18} One study showed that the incidence of FN varied with the type of cancer, for e.g., a higher incidence of 19.8% in lung cancer than that reported in colorectal cancer (9.5%).¹⁹ Another retrospective study by Weycker et al. showed a significant association between FN and chemotherapy, such that up to 21% of patients receiving chemotherapy developed FN.²⁰ Also, as high as half of FN patients develop an infection¹⁵ with an inpatient mortality rate for FN approaching 9.5%.²¹ Nowadays, in the time of COVID-19, the risk is exponentially exaggerated. In fact, one study by Zhang et al. conducted on 28 cancer patients showed worse outcomes, with more than half of the patients (53.6%) having severe disease and 28.6% ultimately dying.²² To avoid such grave consequences, we proposed an algorithm for the outpatient management of febrile neutropenic cancer patients.

Upon presentation to the ED, emergency physicians (EPs) should obtain a thorough medical history and perform a complete physical exam in cancer patients with suspected FN. Concurrently,

Table 1 Criteria for outpatient treatment of febrile neutropenia

Age ≥ 18 years old with no history of non-compliance
No suspicion for life-threatening infective illnesses (sepsis, urinary tract infection, central venous catheter infection... etc.)
No colonization with multi-drug resistant organisms
Not currently on antibiotics
Not on induction chemotherapy & absolute neutrophilic count >100 cells/mm ³
Able to tolerate oral medications/ fluids & not using a feeding tube as the main route for nutrition and medications
Resides within 1-hour travel time from the American University of Beirut Medical Center
Has access to transportation and telephone at residence
No quinolone allergy

the nursing staff should withdraw blood for a full laboratory panel and blood cultures, as well as obtain a urine culture and a chest radiograph. It is important to note that in those with high suspicion of COVID-19, EPs are advised to have a low threshold for performing a high-resolution non-enhanced CT scan of the chest.

Although not yet validated in all cancer patients with COVID-19, we rely on the Multinational Association for Supportive Care in Cancer (MASCC) score²³ in the management of those patients, as it has proven to be valuable in cancer patients with other infections²⁴, and it is logical to assume similar ability in the setting of COVID-19. In conjunction with the MASCC score, we established criteria for the outpatient treatment of febrile neutropenia (Table 1) to identify low-risk patients who are eligible for outpatient management.²⁵⁻²⁷

A patient with a MASCC score ≥ 21 and fulfilling our criteria for outpatient management is given the first dose of the antibiotic in the ED, after consulting the Infectious Diseases (ID), Oncology and Palliative Care teams. The patient is then observed in a separate isolated unit for ≥ 4 hours prior to safe discharge from the ED. The regimen of antibiotics chosen is individualized.

First-line therapy is a combination of oral ciprofloxacin (750 mg) and oral amoxicillin/clavulanic acid 1g, every 12 hours and for 7 days. In case of penicillin allergy, ciprofloxacin (750 mg) every 12 hours along with oral clindamycin (600 mg) every 8 hours, each for 7 days. Second-line therapy is oral levofloxacin (750 mg) for 7 days.

PNEUMONIA

Although the incidence of pneumonia has markedly decreased with the use of adequate prophylactic antibiotics in oncology patients, it remains one of the most feared causes of morbidity and mortality, especially in the light of their neutropenic state.²⁸⁻³⁰ In fact, up to 30% of hospital admissions in cancer patients are complicated with pneumonia.³¹⁻³³

There is little data on the incidence and the causative organisms of pulmonary co-infections and super-infections, such as community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), in COVID-19 patients. In a study by Soriano et al., the authors showed a low incidence of CAP

co-infections (2.1%), HAP super-infections (0.4%) and VAP super-infections (1.1%) in COVID-19 patients.³⁴ They also reported *Streptococcus pneumoniae* and *Staphylococcus aureus* to be the primary causative organisms in COVID-19 patients with CAP co-infections, in contrary to those with HAP and VAP super-infections where *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most isolated organisms.³⁴ In their study, the authors found that patients with CAP co-infections were more likely to be admitted to the intensive care unit (ICU) and that super-infections were mostly seen in patients who were admitted to the ICU.³⁴ In addition, the authors found a higher mortality rate and a prolonged length of stay in COVID-19 patients with super- and/or co-infections.³⁴ In another study by Carratalà et al., similarly low incidence rates of CAP co-infections (3.1%), HAP super-infections (3.1%) and VAP super-infections (1.7%) were documented.³⁵ Besides, the authors found a statically significant association between neutropenia and both co-infections and super-infections; however, ICU admission was only significantly associated with super-infections.³⁵

In the era of COVID-19, it is important to be meticulous with cancer patients presenting to the ED with high suspicion for a co-infection or super-infection. In these patients, especially if neutropenic, we recommend obtaining a high-resolution non-enhanced CT scan of the chest to rule out pneumonia, as this imaging modality is more sensitive than plain chest x-rays in cancer patients and will thus determine the patient's disposition (i.e., admission vs. discharge).^{33,36,37}

When there is high clinical suspicion for pneumonia, patients should be started on treatment without delay. If the patient is eligible for outpatient management (Table 2), the first dose of antibiotics should be given in the ED followed by a brief period of observation prior to discharge. If the temperature drops below 37.8 °C, pulse < 100 beats/minute, systolic blood pressure > 90 mmHg, blood oxygenation > 90 %, and the patient is tolerating oral intake, he/she can be safely discharged to continue the antibiotic regimen at home (Table 3).

PULMONARY EMBOLISM

Venous thromboembolism in cancer patients is

Table 2 Criteria for outpatient management of pneumonia in cancer patients

No recent history of chemoradiation or immunotherapy
No chest radiation in the past month
No history of bone marrow transplantation
No family member having a multi-drug resistant pathogen
No hospitalization for ≥ 2 days within past 3 months
Not neutropenic
Not residing in a nursing home or extended care facility
No antibiotics within past 3 months
No history of high frequency of antibiotic resistance
No chronic dialysis within the last 30 days
Pneumonia Severity Index I or II ³¹

mostly due to a state of acquired hypercoagulability. Also, in solid tumors with a mass effect, increased blood stasis promotes a prothrombotic state. In one study, around 33.3% of oncology patients were found to have an incidental PE upon presentation to the ED.³⁸ Selected cancer patients might be eligible for outpatient management of PE. In Table 4, we suggest a set of criteria for the outpatient treatment of pulmonary embolism in cancer patients.³⁹ This not only improves their QoL and the overall patient satisfaction, but also eliminates the unnecessary risk of contracting infections, namely SARS-CoV-2, that may come along with admissions and prolonged hospitalizations.

Cancer patients with suspected PE are stratified based on the proposed criteria. Those with low-risk PE are offered adequate treatment and observation within the ED, in an isolated setting, after which they are stabilized and discharged. Multiple drug regimens are available, and the choice of a certain anticoagulant over the other is customized and tailored to each patient (Table 5).⁴⁰

It is critical that EPs adequately identify these patients, as the consequences of contracting the virus in cancer patients with PE are drastic. The main concerns in such a scenario include the appropriate use of diagnostic studies, the prothrombotic impact of COVID-19 itself, and the difficult management of co-existing PE and COVID-19 in any given patient. Here, it is imperative to highlight the importance of the pulmonary embolism response teams (PERT) which we have put together. We recommend PERTs to other healthcare facilities, as it offers a multidisciplinary and holistic approach in the management of these patients. This is particularly essential as PE and COVID-19 infection may present similarly, making it even harder to manage.

COVID-19 IN CANCER PATIENTS

There is limited evidence on the incidence, diagnosis, and management of COVID-19 in cancer patients. It is confirmed, however, that the incidence of COVID-19 is markedly higher in cancer patients and has more drastic complications compared to their counterparts of the general population.⁴¹ At AUBMC, general guidelines recommended by the American Society of Clinical Oncology (ASCO) are followed⁴²:

- Educating cancer patients on the disease, its symptoms, and giving them clear return instructions to the ED in case they develop any of the symptoms
- Emphasizing to cancer patients the importance of adopting protective measures, including frequent and adequate handwashing, wearing masks, and self-quarantining
- Strongly urging the ED staff to wear face masks within and outside of the ED setting
- Deferring outpatient clinic appointments and elective surgeries for cancer patients. Elective

Table 3 Outpatient antibiotic regimen for pneumonia in cancer patients

First line	Amoxicillin/ clavulanate (875/125 mg every 8 hours) and oral azithromycin (first dose 500 mg, then 250 mg daily for subsequent doses)
In case of intolerance to macrolides	Amoxicillin/ clavulanate (875/125 mg every 8 hours) and oral doxycycline 100 mg every 12 hours
In case of penicillin allergy	Oral levofloxacin 750 mg once daily

Table 4 Criteria for outpatient treatment of pulmonary embolism in cancer patients

Age < 80 years old
 Not including comorbidities such as ischemic heart disease, congestive heart failure, chronic lung disease, chronic kidney disease, liver disease, thrombocytopenia
 No clinical suspicion of deep vein thrombosis (DVT)
 Normal vitals
 SaO2 > 94 %
 Undetectable troponin
 Normal Brain natriuretic peptide (BNP) levels
 Normal mental status with good understanding of risks and benefits and have good home support
 No thrombolysis needed and no contraindication to anticoagulation
 No PE while anticoagulated
 Less than 2 doses of IV narcotics for pain control
 Not pregnant

surgeries should be well differentiated from non-emergent but essential cancer surgeries (i.e., for cancers that impose high risks of morbidity and mortality if the surgery is delayed).⁴³

- Delaying cancer screening appointments to preserve resources and limit exposure, except in cases of high suspicion.⁴⁴
- Initiating telehealth to provide patients, particularly those with cancer, with adequate healthcare from within their homes.

Prevalence

The prevalence of cancer in COVID-19 positive patients is highly variable. Although no definite numbers have been reported in Lebanon, numbers from different countries hint at a high prevalence and thus stress on the need for special care in oncology patients. Studies from China (Wuhan), United States (New York), and Italy (Lombardy)

showed a prevalence of up to 2%, 6%, and 8%, respectively.^{11,45,46} Moreover, 20% of mortalities from COVID-19 in Italy were in those with active cancer.⁴⁷

Clinical Presentation

The clinical picture of COVID-19 in oncology patients mirrors that of the general population. It includes fever, chills, cough, shortness of breath, fatigue, myalgias, headache, sore throat, diarrhea, and loss of taste and smell sensations. However, present or past history of cancer might place patients at a risk of a more severe disease.¹² Studies have repeatedly shown that the risks of morbidity and mortality from COVID-19 are significantly higher among oncology patients, predominantly those with liquid tumors, lung cancer, and advanced/ metastatic disease.^{10,48-52} Moreover, four retrospective studies, all done in Wuhan, China, showed that patients who received cancer treatment within a month from

Table 5 Drug regimens for the outpatient treatment of pulmonary embolism in cancer patients

Drug	Dose	Contraindication
Enoxaparin (Lovenox)	1 mg/kg every 12 hours	Avoid when GFR <30 ml/min
Dabigatran (Pradaxa)	150 mg (oral) every 12 hours after 10 days of low molecular weight heparin	Avoid when GFR <30 ml/min Avoid use with PGP inhibitors and inducers*
Rivaroxaban (Xarelto)	15 mg (oral) every 12 hours for 21 days then 20 mg daily	Avoid when GFR <30 ml/min Avoid use in severe hepatic impairment (affects INR)
Apixaban (Eliquis)	10 mg (oral) every 12 hours for 10 days then 5 mg every 12 hours	Avoid in GFR <25 ml/min Avoid use in severe hepatic impairment

* P-Glycoprotein (PGP) inhibitors as azithromycin, amiodarone, verapamil and inducers as vinblastine, dexamethasone, carbamazepine

presentation for COVID-19 were four times more likely to die in the hospital.⁵³ On the other hand, other internationally conducted studies refuted an association between active cancer treatment and mortality from COVID-19.^{54,55}

Screening for COVID-19 in Cancer Patients

Timely and adequate management of COVID-19, especially in a vulnerable population like cancer patients, is highly important. This, however, does not necessarily mean that we should obtain a reverse-transcriptase polymerase chain reaction (RT-PCR) from the upper respiratory tract from every cancer patient presenting to our ED. We have thus specified those that should be screened, as follows:

- Having COVID-19 symptoms
- Were exposed to a suspected/ confirmed COVID-19 case
- Requiring hospital admission
- Scheduled for an elective surgery
- Being two to three days prior to the initiation of immunosuppressive therapy and/or undergoing medical interventions (solid organ transplantation, bone marrow transplantation...)

Approach to COVID-19 Positive Cancer Patients

The management of COVID-19 in cancer patients is identical to that in non-cancer patients. Patients with mild or no symptoms can be cared for conservatively while they quarantine themselves at their homes.¹² Hospital admissions and extensive medical care, on the other hand, are provided to those with severe infection.

Anti-COVID-19 Agents Used in Hospitalized Cancer Patients

In general, the recommended treatment regimens for COVID-19 patients with cancer are similar to those used in the general population.⁵⁶ The choice of anti-COVID-19 agents is mainly dependent on the requirement for oxygen supplementation and the extent of oxygen requirements.

In hospitalized COVID-positive cancer patients not requiring supplemental oxygen, dexamethasone and other corticosteroids are recommended against.⁵⁶ The rationale behind this emerged from the *RECOVERY* trial, where hospitalized COVID-19 patients who did not require oxygen supplementation

were randomized to receive either dexamethasone with the standard of care or the standard of care alone.⁵⁷ Results showed no survival benefit for those who received dexamethasone, such that 17.8% of subjects who received dexamethasone and 14% of those who did not, died within one month.⁵⁷ In contrary, those who do have oxygen requirements, the following are suggested: (a) remdesivir alone in those with minimal oxygen requirements and (b) remdesivir plus dexamethasone for those with increased oxygen requirements.⁵⁶

In hospitalized COVID-positive cancer patients who require oxygen through a high-flow device or non-invasive ventilation, dexamethasone or dexamethasone combined with remdesivir can be used.⁵⁶ For those, in cases of rapidly increasing oxygen needs, baricitinib or IV tocilizumab may be added.⁵⁶ In hospitalized patients requiring mechanical ventilation, dexamethasone is recommended.⁵⁶ From those, patients requiring ICU admission within the next 24 hours, IV tocilizumab may be added to dexamethasone.⁵⁶

In another study, the treatment options that were studied were as follows: (1) combined hydroxychloroquine and azithromycin, (2) combined hydroxychloroquine, azithromycin, and high-dose steroids, (3) combined hydroxychloroquine and tocilizumab, (4) combined hydroxychloroquine, azithromycin, and tocilizumab, (5) hydroxychloroquine alone, (6) azithromycin alone, (7) high-dose steroids alone, and (8) remdesivir alone.

Remdesivir taken alone was the only regimen found to be significantly associated with a decreased 30-day all-cause mortality when compared with other regimens (OR 0.41, 95% CI [0.17-0.99]), but not when compared to no anti-COVID-19 treatment (OR 0.76, 95% CI [0.31-1.85]).⁵⁸ On the other hand, the only high-dose steroids regimen was associated with increased 30-day mortality compared to no anti-COVID-19 treatment, but the difference was not significant (OR 2.8, 95% CI [0.77-10.15]).⁵⁸ Likewise, hydroxychloroquine combined with any other agent significantly increased mortality when compared with other treatment regimens and when compared to the no treatment group.⁵⁸ Nevertheless, hydroxychloroquine alone was not associated with an increased mortality rate.⁵⁸

In addition, in one interesting study, the use of anti-COVID-19 agents in patients receiving anti-CD20 for their cancer was explored. In one patient receiving rituximab for lymphoma, rapid recovery was achieved.⁵⁹ This was explained by the possible formation of antibodies that replaced those depleted by rituximab. This, however, raised the concern of ineffective COVID-19 vaccination in patients receiving anti-CD20, as those agents weaken the humoral immune response.⁴¹

Physician-Patient Communication

In cancer patients found to be COVID-positive, the patient's primary care physician, emergency physician, and oncologist should work hand in hand to offer appropriate medical care. A proper management plan that emphasizes the goals of care should be discussed by a multidisciplinary team, together with the patient and his/her family. This is especially important in patients with late-stage disease or those with significant comorbidities who contract SARS-CoV-2 infection and eventually require mechanical ventilation, as outcomes are thought to be worse.⁶⁰ The role of palliative care in such a setting is extremely valuable.

LIMITATIONS

The review at hand sheds light on the importance of outpatient management of cancer patients during the COVID-19 pandemic. It describes protocols that were safely implemented at our institution - AUBMC, distinguished for its high-quality cancer care and its well-equipped cancer center. However, our management plans were merely based on the clinical expertise of emergency physicians that have done their fellowships in oncology and palliative care, as well as the combined decision of these physicians and patients' oncologists. Although not validated, our plans have shown a promising and effective capacity to treat cancer patients on an outpatient basis during the COVID-19 pandemic, and perhaps during future pandemics. It should also be highlighted that the clinical decisions were guided by evidence available at the time of implementation of the discussed approaches.

CONCLUSION

The management of cancer patients in light of the COVID-19 pandemic imposes a real challenge

on clinicians, especially emergency physicians. As cancer patients continue to rely on emergency departments to access the care they need, it is imperative that emergency physicians adequately screen those presenting with signs and symptoms of COVID-19. To limit their exposure to SARS-CoV-2, cancer patients eligible for outpatient management should be discharged safely from the ED after receiving adequate medical care. At AUBMC, well-defined criteria for the outpatient management of the most common causes of ED presentations in cancer patients have been proposed and used. As for cancer patients who develop COVID-19 infection, management should be individualized, while properly weighing the risks versus the benefits of any adopted treatment plan.

Conflict of interest: authors declare no conflict of interest related to this manuscript.

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