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Treatment of Cancer Patients in the Era of the Covid-19 Pandemic

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ABSTRACT
Covid Disease 2019 (COVID-19) is a flare-up of respiratory infection brought about by novel Covid and has arrived at pandemic state. Disease patients have increment vulnerability to contamination brought about by the actual threat and anticancer foundational treatment. In light of individual patient evaluation, the oncologist's choice with respect to the requirement for guaranteed oncological mediation characterizes patients into 'critical' and 'non-earnest' conditions. Thought of chance and advantage for dynamic mediation in the malignant growth populace during an irresistible sickness pandemic should be individualized. Thought for deferring elective medical procedure or chemotherapy for malignant growth patients with generally safe of movement ought to be viewed as dependent upon the situation. Choices for treating or postponing treatment are best talked about with the patient with regards to multidisciplinary care.

Keywords: COVID-19, Hematology malignancy, Cancer

I. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an outbreak of respiratory disease caused by novel coronavirus that was first detected in China and has now spread to more than 150 countries. This disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This type of respiratory disease, characterized by rapid human-to-human transmission, and has reached a pandemic spread [1

The transmission of respiratory pathogens have been associated with three primary modes known as "contact," "droplet," and "airborne" transmission. The airborne or aerosol transmission occurs via small respiratory droplets or droplet nuclei, less than 10 μm in diameter, which remains airborne for sufficient time to transmit the pathogen and may get deposited deep into the respiratory tract, including alveolar region. However, it is also being speculated that the particles of various sizes but indistinct behavior are produced in continuum during the respiratory activities of the infected person and particles as large as 50 μm can also remain airborne and travel the considerable distance as per the factors including force and volume of exhalation, airflow, temperature and humidity. Furthermore, it should not be neglected that the aerosols are generated even from activities such as exhalation, coughing, sneezing and talking by the infected individuals [2].

Until now, nearest millions confirmed cases of COVID-19 have been recorded including 6,108,976 deaths reported by the World Health Organization as of 26 March 2022 [3].

In a study including 1,524 patients with cancer, cancer survivors have twofold increased risk of COVID-19 infection when compared to the general population. In another series from one institution in the Wuhan area, the SARS-CoV-2 infection rate in patients with cancer was 0.79% (95% CI = 0.3-1.2), higher than the cumulative incidence of all diagnosed COVID-19 cases and reported over the same time period (0.37%, 41,152/11,081,000 cases, 17 February 2020). The commission WHO-China on COVID-19 identified a significantly higher case fatality rate among patients with pre-existing malignancies (7.6%) compared to patients without comorbid conditions (1.4%) [1].

Impact of the Covid-19 Pandemic on Cancer Treatment

The potential misfortune brought about by COVID-19 is something like triple in oncology patients. To begin with, as far as vulnerability to disease brought about by the actual harm and anticancer fundamental treatment. Second, the impact of defer in careful cancer resection and organization of anticancer foundational treatment on the drawn out endurance of this gathering is obscure; it is likewise obscure the way in which long this postpone will be occur. At last, those with malignant growth might encounter difficulties as to whom basic consideration and restricted ventilated beds ought to be distributed, when contrasted with

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those without critical comorbidities, for example, disease [4].

Oncologists are advised to prioritize cancer patients for examination at a cancer clinic or center based on the patient's current cancer status and their risk for COVID-19 infection. Several factors must be considered, such as the stage of the cancer and the patient's tumor grade, the characteristics of the tumor and the tumor burden. Based on individual patient assessment, the oncologist's decision regarding the need for immediate oncological intervention classifies patients into 'urgent' and 'non-urgent' conditions [5]

Instances of malignant growth patients with critical circumstances are those with beginning phase or locally creating disease who have not finished therapy and are qualified for a medical procedure, adjuvant chemotherapy, radiation treatment, hormonal and biologic treatment. Patients with cutting edge illness with an enormous cancer trouble who are presently indicative and those with oncological crises are likewise included. These patients might require prompt treatment and may require oncological intercession as postponing treatment will diminish their endurance, yet considering that the choice to encourage the patient to come to the medical clinic should be offset with the gamble of the COVID-19 contamination. Then again, patients with stable infection, who are asymptomatic and have finished disease treatment, are named non-pressing patients who might require a less forceful methodology and facility visits might be deferred [5].

It is almost impossible to develop recommendations that can be applied to all cases. The complexity of the patient and disease varies in different scenarios. In the decision-making process, it is also important to consider the working conditions of the healthcare professional team and the availability of resources. Medical staff isolation measures, restrictions on face-to-face meetings, and the loss of professionals affected by COVID-19 are additional difficulties. Given this situation, maintaining a virtual tumor committee can be very useful. A variety of existing communication tools can be used, providing space to discuss cases with the participation of a multidisciplinary team [6].

There is no "one-fits-all" approach to providing cancer care during the COVID-19 pandemic, and there are no international guidelines [6]. Options for treating or delaying treatment are best discussed with the patient in the context of multidisciplinary care. The final decision must be made after thorough discussion with the patient and informed consent [5].

Treatmentof Cancer Patients in the Era of the Covid-19 Pandemice

Surgery

The United States Centers for Disease Control and Prevention's guidelines for health care facilities and guidelines from the World Health Organization suggest that "elective surgery" in inpatient facilities should be rescheduled, if possible. However, doctors and patients need to make their own decisions, based on the potential dangers of delaying the required cancer-related surgery; in most cases, these surgery cannot be considered "elective". Some have distinguished the non-emergency part of cancer surgery as "essential cancer surgery", including surgical management of brain tumors, as well as resection of the breast, colon, stomach, pancreas, liver, bladder, kidney, and lung. These are generally cancers that cannot wait two or three months, and the patient has a significant chance of benefiting from surgery [7].

In solid cancer patients, the main treatment option in the early stages is surgery. In patients with colorectal cancer, survival is 3-10 years lower if therapy is started more than 90 days from diagnosis. The ideal time, especially for colon cancer resection, is estimated to be between 3 to 6 weeks from diagnosis, which is unlikely to be achieved during the COVID-19 pandemic. This will have an impact on the quality of care that can result in a decline in short-term and long-term cancer treatment outcomes. Increased waiting time for therapy is associated with increased treatment costs [8].

The American College of Surgeons has decided on this approach, given that cases involving cancer that can progress without treatment should be undertaken to minimize the need for emergency procedures, which are often more complicated. In addition, another category of essential surgery is selective palliative procedures to relieve pain and suffering or acute neurological deficits that cannot be treated. However, if an operation requires postoperative intensive care, the available Intensive Care Unit (ICU) capacity should be considered as part of the decision [4]. In addition, the risks of surgery may carry the risk of nosocomial infection with pandemic pathogens [1]. The outcome of surgery during the COVID-19 pandemic has been described in an observational study of 1,128 patients who underwent surgery between

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January 1 and March 31, 2020, all of whom had confirmed SARS-CoV-2 infection within 7 days before or 30 days after surgery. Overall, 30-day mortality was 24%, most of which (83%) was due to pulmonary complications [6]. The following are recommendations from the American College of Surgeons and other groups to resume elective surgery: [7]

- SARS-CoV-2 infection rates should be on a downward trend for at least two weeks in the geographic location of the facility.
- Utilization of resources, including ICU beds and personal protective equipment, must be carefully calibrated.
- Testing on patients and employees should be highly considered.
- Prioritization and scheduling of cases must be carefully managed by all key stakeholders.

Radiation therapy

Some patients receiving Radiation Therapy (RT) for curative purposes or for rapidly growing tumors may continue therapy, because the risk of delaying therapy is greater than the risk of COVID-19. If available, an alternative RT regimen should be offered. For example, international expert consensus statements have recommended that short-term neoadjuvant RT be preferred over long-term chemoradiotherapy for patients with advanced rectal cancer during the pandemic [7]. For those receiving RT for symptom control, or for whom schedule changes do not have a significant impact on outcome outcome, treatment should be delayed or adjusted [8]. For patients with stable cancer, radiotherapy treatment may be delayed for up to 4-8 weeks [7]. If a hypofraction schedule is appropriate for a particular condition, should be considered and this approach is consistent with the guidelines of the American Society for Radiation Oncology (ASTRO) [7].

In patients with suspected or confirmed SARS-CoV-2 infection, radiotherapy may be discontinued or continued as long as their illness is mild to prevent potential spread to other patients and staff. On the other hand, in cases with significant viral symptoms, treatment should be discontinued and continued only after the patient has recovered.

In patients who are actively undergoing RT with a defined treatment plan, the decision to continue requires careful consideration of the indications, dosages given, and risks and benefits [9]. Increasing the use of radiotherapy should be considered, because this modality does not compete with resources required for the management of COVID-19, and can be completed within a few therapy visits (usually 1-5) in an outpatient setting. These treatments are generally less immunosuppressive than other therapeutic modalities [10]. ASTRO suggests that canceling or delaying cancer treatment may be an appropriate option for patients with COVID-19, after a reassessment of the patient's situation [7].

If patient develops symptoms of cough, fever, or shortness of breath, the patient should wear a protective mask and radiotherapy can be continued. If a new cancer patient tests positive for COVID-19, do not start treatment. If a patient undergoing treatment is suspected of having COVID-19, following the onset of typical COVID-19 symptoms and currently awaiting a microbiological diagnosis, they should discontinue treatment. If a patient undergoing treatment tests positive for COVID-19 and is usually symptomatic, they should stop treatment. If patients undergoing treatment test positive for COVID-19 but are asymptomatic, they must stop treatment [8].

Anticancer systemic therapy

There is no direct evidence to support change or delay chemotherapy or immunotherapy in cancer patients. Maintaining anticancer routinely or potentially immunosuppressive therapies is not recommended for those who do not have COVID-19. The balance of the potential harm of delaying or discontinuing treatment versus the benefits of possibly preventing SARS-CoV-2-19 infection is highly uncertain. The American Society of Clinical Oncology (ASCO) recommends that clinical decisions be made on an individual basis taking into account factors such as cancer curing ability; risk of cancer recurrence with delay, modification, or discontinuation of treatment; the number of therapy cycles completed; and patient tolerance for treatment. The incidence of local viral infection and the availability of the necessary resources, and whether testing for SARS-CoV-2 has been carried out are also considerations [7].

Chemotherapy: During a pandemic, the potential benefits with chemotherapy will not change, but the risk of harm will increase to a degree that cannot be easily quantified. Patients who underwent chemotherapy or surgery in the month before being diagnosed with COVID-19 had a numerically higher risk (three out of four patients) of a severe clinical event than those who did not receive chemotherapy or surgery (six of14 patients) [1].

However, contrary to this statement, study by Lee, et al. using a multivariate analysis concluded that cytotoxic chemotherapy given within 4 weeks of confirmed COVID-19 was not a significant contributor to more severe disease or a predictor of death from COVID- 19, compared with cancer patients who did not

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receive chemotherapy during that period. This study concluded that mortality from COVID-19 in cancer patients appears to be driven primarily by age, gender, and comorbidities [11].

Cancer patients receiving cytotoxic chemotherapy are at high risk for infectious complications, mainly because of its effects on myeloproliferative cells in the bone marrow, as well as on rapidly dividing cells including intestinal mucosal cells leading to disruption of the protective barrier. Therefore, patients receiving active chemotherapy will often develop neutropenia and up to 5-30% of patients may develop febrile neutropenia.

Also consider intermittent chemotherapy or discontinuation of treatment for eligible patients. This approach is common in oncology practice, especially in metastatic states or in patients with deep remission. The use of intermittent chemotherapy does not appear to produce a poor outcome, according to a study conducted in patients with metastatic colorectal cancer [12,13].

However, in some cases, delaying treatment can lead to worsening symptoms and performance status and missed opportunities for treatment. Considerations should include whether the delay necessitates hospitalization for symptom relief, which will further emphasize available resources. Joint decision making is essential [7].

The considerations for chemotherapy treatment during the COVID-19 pandemic set by ASCO are as follows: [7]

• For patients in remission receiving maintenance therapy, stopping chemotherapy may be an option.

• Oral chemotherapy and home infusion of chemotherapy drugs (if logistically possible) may be an option for some people, but requires coordination with the oncology team to ensure that patients are properly treated. Oncologists may consider home treatment for supportive care, such as hydration or antiemetics.

• If a particular cancer center is severely affected by corona virus infection, it is necessary to change the chemotherapy schedule so it can reduce the number of visits.

Immune checkpoint inhibitor immunotherapy: Currently, there is not enough data on whether Immune Checkpoint Inhibitor (ICI) therapy affects the severity of COVID-19, and results are conflicting [7].

It is inconclusive whether ICI therapy is highly immunosuppressive. Avoiding it in cancer patients to reduce coronavirus infection could dissuade these patients from the highly active class of drugs. Special consideration should be given to patients being treated for immune-related adverse events who are exposed to immunosuppressive agents over a long period of time [12].

In addition to concerns that ICI therapy may worsen the clinical course of COVID-19 because the immune response is enhanced by this therapy, there is also concern that COVID-19 may affect the diagnosis and treatment of ICI-related side effects. Of particular concern is treatment-associated pneumonitis, which can mimic COVID-19 and increase the risk of serious complications if the patient develops COVID-19. In addition, given that glucocorticoids are against for mild to moderate COVID-19 but are used to manage ICI-associated pneumonitis, diagnostic uncertainty may delay appropriate management of severe conditions. For individuals with a known diagnosis or exposure to COVID-19, it is advised to withhold treatment until it is clear that the patient will not develop COVID-19 [7].

Less frequent administration of medication is an option for patients already receiving medication. One modeling study showed that pembrolizumab 400 mg every six weeks caused the same exposure as a single dose of 200 mg or 2 mg/kg every three weeks. The safety and efficacy of this extended dose option have been demonstrated in patients with advanced melanoma, and it is an appropriate choice for some patients receiving pembrolizumab monotherapy, particularly in areas where the prevalence of SARS-CoV-2 is high.

The decision about whether to use combination versus single agent immunotherapy needs to be reviewed on an individual basis. The risk of immune-related adverse events associated with combination regimens containing ipilimumab (or other combination immunotherapy), including the associated risk of hospitalization and exposure to COVID-19, must be weighed against the reduced efficacy of single-agent therapy in each particular setting. Other considerations are similar to those receiving chemotherapy [7].

Monoclonal Antibody Anti-CD20: Lymphopenia appears to be a specific risk factor for poor outcome from COVID-19 and other coronaviruses. This has led several expert groups, including the European Society for Medical Oncology (ESMO) to recommend a re-evaluation of the need for drugs that inhibit B cells, such as anti-CD20 monoclonal antibodies, during the pandemic, especially optional treatments such as maintenance therapy for follicular lymphoma. On the other hand, guidelines from the American Society of Hematology (ASH) state that rituximab continues to be prescribed by some doctors, but not others. Some have discontinued maintenance rituximab, particularly in older patients and younger patients with low immunoglobulin levels [7].

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 498-504 www.ijprajournal.com ISSN: 2249-7781

In addition, Houot, et al. also hypothesized that there is a significant risk for anti-CD20 therapy to reduce the efficacy of future SARS-CoV-2 vaccines. Anti-CD20 antibodies trigger a rapid and prolonged depletion of B cells that can harm the immune system. Consistent with the immunosuppressive effect of anti-CD20 antibodies, rituximab has been associated with a risk of latent viral reactivation, particularly hepatitis B virus infection and progressive multifocal leukoencephalopathy caused by reactivation of latent JC virus. Anti-CD20 therapy also resulted in impaired humoral immune response secondary to vaccination. B cells are required for the development of the humoral immune response to neoantigens and B cell depletion following rituximab administration appears to reduce the humoral immune response to neoantigens, of which COVID-19 is one of the reason [14]. Both T-cell dependent and independent responses have been shown to be significantly impaired at least during 6 months after rituximab therapy. For this reason, most guidelines recommend waiting at least 6 months after a rituximab infusion to get vaccinated [15].

Allogeneic Hematopoietic Cell Transplant: Hematopoietic Stem Cell Transplant (HSCT) recipients are at increased risk of various infections. HSCT patients receive therapy that results in prolonged cytopenia, making transplant patients infected with COVID-19 particularly susceptible to severe symptoms. Considering these profound implications, the European Society for Blood and Marrow Transplantation (EBMT) recommends careful evaluation at- risk recipients, and in appropriate cases, delaying transplant therapy until paatient show no symtpoms (Table 1) [15].

Table 1: European Community Recommendations for Blood and Bone Marrow Transplantation regarding the diagnosis of SARS-CoV-2. **View Table 1**

On the other hand, patients with aggressive blood malignancies have an urgency for life-saving therapy. Stem cell transplantation and cellular immunotherapy provide curative treatment in this aggressive disease and cannot be delayed. Cryopreservation of donor products is recommended because of travel restrictions that limit access to international donors for allogeneic stem cell transplantation. Therapy can be adjusted by reducing immunosuppression, transferring patients from inpatients to outpatient clinics, and delaying treatment [8].

Although there are limited data on the impact of COVID-19 on transplant candidates and donors and recipients of cellular therapy, there is considerable concern that COVID-19 could have a significant impact on post-transplant or post-therapy outcomes. The decision about whether hematopoietic cell transplantation should be postponed should be made on an individual basis. Considerations from ASCO include: [7]

- It may be prudent to test for COVID-19 on potential donors even in the absence of evidence of transmission by blood transfusion.
- As a general precaution, post-transplant visits may need to be limited and visitors may need to be screened for symptoms and possible exposures.

Supportive Care of Cancer Patients in the Era of Covid-19 Pandemic

American Society of Clinical Oncology (ASCO) have established the following recommendations for supportive care during cancer therapy: [7]

• The role of prophylactic antiviral therapy for COVID-19 is unknown in any patient, including immune compromised patients.

• Port flushing may occur at intervals of every 12 weeks and patients who are able to rinse their own device should be encouraged to do so. However, the training process itself can be a source of exposure and access to home sterilization supplies is limited.

• Transfusions should be given according to usual practice guidelines if possible, with consideration of an erythropoietin-stimulating agent if severe or life-threatening anemia is anticipated, or if blood products are scarce due to lack of donation.

• For patients who present with fever and tend to be neutropenic based on the time of their cancer treatment, empiric antibiotics may be prescribed if the patient appears stable by clinical assessment (in person or via telemedicine evaluation).

• Although myeloid growth factor support is usually provided for those at high risk of febrile neutropenia (> 20%), patients at lower risk may be prescribed growth factor prophylaxis during the pandemic.

Glucocorticoid

Glucocorticoids are widely used in cancer patients, for example, for nausea and vomiting caused by chemotherapy or radiation; infusion- related reactions; management of edema in patients with brain metastases or epidural spinal cord compression; and in conjunction with hormone therapy such as abiraterone, to reduce the likelihood of treatment-related mineralocorticoid deficiency [7].

Managing subcutaneous ports

The typical frequency for subcutaneous port maintenance flushing is every four to six weeks.

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However, some data suggest that extending the interval of port maintenance flushing implanted in adult oncology patients to every 12 weeks is still safe and effective. Patients who are able to rinse the device themselves may be encouraged to do so. However, the training process itself can be a source of exposure, and access to sterile supplies at home may be limited [7].

Early treatment planning

Proactive early treatment planning is important for all cancer patients, but especially important given the added risk of COVID-19. Aligning the care provided with the values and goals of patient care in acute life-threatening illness is important, especially for patients with life-limiting chronic illnesses. Individuals most likely to develop severe disease will be older and have a greater burden of chronic disease. This is a population that may wish to give up extended life support, if needed. If an oncology patient with advanced disease or with significant comorbidities affecting the heart or lungs develops COVID-19 and requires mechanical ventilation, the prognosis is likely to be poor [7].

It is very important to proactively discuss with patients about early treatment planning, especially for those with advanced cancer. This should include the use of advance hints or other expressions of end-of-life preferences as well as clear documentation of the conversation, especially if it takes place during a tele health consultation [1,7**ological Research in the Era of the Covid-19 Pandemic**

Oncological Research in the Era of Covid-19 Pandemic

New limitations and constraints have emerged with the pandemic, including the need to limit hospital admissions of clinical trial participants. Four questions arose such as the suitability of starting a new clinical trial, eligible patients for inclusion, patients already enrolled, and clinical trial participants who contracted COVID-19 infection.

Regarding new inclusion in ongoing clinical trials, the expert consensus guidelines recommend deferral, which has been agreed by most scientific groups (except for clinical contexts without conventional therapy and taking into account the benefits-risks associated with COVID-19). For the patients who have been included in the trial, the issue is ensuring safety. Clinical trials require frequent attendance and additional examinations on top of standard care, increasing the risk of COVID-19 infection. The suitability of starting a new trial should be assessed by the sponsor and principal investigator, with priority given to trials related to the management of patients infected with SARS-CoV-2.

Early-phase clinical trials in oncology, especially drugs for which patient benefits have not been proven, should not be initiated. For patients who contracted COVID-19 while enrolled in trials, global guidelines do not predict recalls, unlike the International Gynecologic Cancer Society. Pharmacists may here refer to trial protocols to identify iatrogenic risks between COVID-19 treatment and trial therapy [16].

II. SUMMARY

The limited but accumulating evidence suggests that patients with cancer are at higher risk of COVID-19 infection than individuals without cancer. The main management strategies for patients with cancer in this COVID-19 pandemic include clear communication and education about hand hygiene, infection control measures, high-risk exposure, and the signs and symptoms of the COVID-19. Consideration of risk and benefit for active intervention in the cancer population during an infectious disease pandemic must be individualized. Consideration for postponing elective surgery or chemotherapy for cancer patients with low risk of progression should be considered on a case-by-case basis. Minimizing outpatients' visits and elective admissions can help in mitigating exposure and possible further transmission. Telemedicine may be used to support patients during an infectious pandemic to minimize visits and risk of exposure. More research is needed to further understand SARS-CoV-2 virology and epidemiology in the cancer population.

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