Infect Chemother. 2020 Dec;52(4):496-502
https://doi.org/10.3947/ic.2020.52.4.496
pISSN 2093-2340·eISSN 2092-6448

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Review Article

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Decision on Chemotherapy amidst COVID-19 Pandemic: A Review and a Practical Approach from Iran

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OPEN ACCESS

Received: Oct 6, 2020
Accepted: Nov 15, 2020

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Conflict of Interest
No conflicts of interest.

Author Contributions
Conceptualization: AR. Data curation: AR, SA. Investigation: AR, FTH. Methodology: FTH. Project administration: AR. Resources: AR, FTH. Software: FTH. Supervision: AR.

ABSTRACT

To provide a step-by-step approach to chemotherapy (CTx) in the novel coronavirus disease 2019 (COVID-19) era. The COVID-19 pandemic is the current global issue resulting in vast health implications. Amid the COVID-19 era, special attention must be paid to at-risk groups, including patients with cancer. To our knowledge, there is a paucity of data on the decision for CTx during the pandemic. We herein provide practical recommendations on the CTx of cancer patients over the pandemic based on our experience in an educational hospital. The decision on CTx should be considered to be individualized based on clinical findings. We hope that our experience provides a practical guide for clinical oncologists to deliver more effective cancer care over the COVID-19 pandemic.

Keywords: Cancer; Chemotherapy; COVID-19

INTRODUCTION

Since December 2019, the novel coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to global catastrophe. It has led to 852,710 deaths worldwide up to September 1, 2020, with an average crude mortality rate of 3 - 4% [1, 2]. Meanwhile, patients with cancer receiving chemotherapy (CTx) need special attention due to a possible increased risk of mortality for their common immunocompromised status [3, 4]. Amid the COVID-19 pandemic, cancer centers around the world have tried to address protocols for better management of cancer [5-9]. To our knowledge, however, the peculiar protocol for CTx during the pandemic has rarely been evaluated directly. The aim of this paper is to describe the experience of the Clinical Oncology Department of Shohada-e Tajrish Hospital to provide a practical approach to CTx during the COVID-19 era.

SPECIAL CONSIDERATIONS FOR CTX AMIDST COVID-19 PANDEMIC

Notwithstanding the conflicting reports defining the CTx as a risk factor for COVID-19 mortality [3, 10], patients with cancer receiving CTx need special considerations due to their

Validation: AR, SA, FTH. Visualization: FTH. Writing - original draft: FTH. Writing - review & editing: FTH.

immunocompromised status. These considerations may be classified into: 1) before the onset of CTx course, 2) during infusion of chemotherapeutics, 3) between CTx cycles, and 4) after the end of CTx course. In all four stages, effective personal protective equipment (PPE) and social distancing are recommended.

1. Before the onset of the chemotherapy course

- Screen patients for signs and symptoms (S/S) of COVID-19 with high sensitivity (including fever [temperature ≥ 38°C or 100.4°F], fatigue, dry cough, myalgia or arthralgia, sore throat, and headache) and high specificity (including dyspnea or chest tightness, hypoxia, loss of smell or taste, nausea or vomiting [N/V], diarrhea, and shivering or chills) [11].
- Consider alternative choices with less toxicity. For example, neoadjuvant endocrine therapy for eligible patients with breast cancer [12].
- Choose less myelosuppressive CTx regimens. For example, 4 cycles of docetaxel plus cyclophosphamide instead of the 8 cycles of anthracycline-based regimens as the adjuvant CTx of patients with low-risk breast cancer [13]. Likewise, combination CTx can be changed to single agents, if applicable.
- Apply CTx regimens minimizing patient's exposure to healthcare personnel. For example, CAPOX (capecitabine and oxaliplatin) is preferred over FOLFOX (fluorouracil, leucovorin, and oxaliplatin) as the adjuvant CTx of locally-advanced rectal cancer [7]. Moreover, switch over from intravenous to oral therapy further decreases patient's exposure.
- In the metastatic setting, withhold CTx if it does not improve survival.

2. During infusion of chemotherapeutics

Administer CTx agents in a specified ward with special considerations, including dedicated healthcare personnel, the adequate distance between patients (≥2 meters) [14], and appropriate air conditioning systems [15]. Moreover, the presence of patient attendants in the treatment room must be limited. These preparations decrease the probability of SARS-CoV-2 transmission.

3. Between chemotherapy cycles

- Use virtual visits (*e.g.*, telephone visit) for managing CTx side effects and evaluation of nadir complete blood count (CBC).
- Considering the importance of the innate immune system in the initial clearance of SARS-CoV-2, prescribe granulocyte-colony stimulating factor (G-CSF) for regimens with high- to intermediate-risk of febrile neutropenia (likelihood >10%) [5].
- Before each CTx cycle, evaluate patients for S/S of COVID-19 (as mentioned above).
- The physician needs to distinguish the side effects of CTx overlapping common S/S of COVID-19. The following paragraphs explore the specific features of the three most common CTx side effects in detail:

(1) myalgia and arthralgia: taxane CTx has greater incidences of myalgia and arthralgia than non-taxane forms of CTx [16]. Taxane-associated pain is in two forms: a) acute pain syndrome, and b) neurotoxicity-associated pain. Acute pain syndrome develops in 1 - 2 days that usually lasts for 1 week, and is characterized as diffuse, achy myalgias and/or arthralgias usually responsive to common analgesics (*i.e.*, NSAIDs and opioids) [17]. Neurotoxicity-associated pain is characterized as chronic, spastic pain -usually associated with paresthesia- that may respond to prednisone, gabapentin, or Shakuyaku-kanzo (a Japanese herbal medicine) [16, 18]. Myalgia in COVID-19 is due to intracellular lactate accumulation and is characterized as generalized pain (especially in the lower back), which is resistant to conventional painkillers and resolves after

https://doi.org/10.3947/ic.2020.52.4.496

a decrease of viral load [19]. Associated S/S may further help to differentiate it from CTx-induced myalgia.

(2) dry cough: the list of CTx agents damaging lung parenchyma is growing. However, it is more common in a few agents include cyclophosphamide, bleomycin, and methotrexate [20]. During the pandemic, true CTx-induced pulmonary toxicity must be differentiated from COVID-19-induced lung injury. The histopathologic feature of CTx-induced lung damage is common, with swelling of endothelial cells, destruction of type I pneumocytes, and proliferation of type II pneumocytes [20]. However, microscopic evaluations of lung parenchyma have demonstrated distinct features in COVID-19, with diffuse alveolar damage, intra-alveolar neutrophil infiltration, hyaline membrane formation, and intra-alveolar hemorrhage [21]. Despite these differences, the clinical features are almost similar. To differentiate, radiographic features may be helpful. The most common radiographic abnormality of COVID-19 is airspace opacities, commonly in the form of bilateral, peripheral, and basilar consolidations [22]. However, the radiographic features of CTx-induced pulmonary toxicities depend on the agents (*e.g.*, bibasilar reticular pattern with pulmonary edema in cyclophosphamide, interstitial infiltrates with hilar and mediastinal lymphadenopathy in methotrexate, etc.) [20].

(3) nausea and vomiting: N/V are the early symptom of COVID-19 [23]. To differentiate it from the CTx-induced N/V (CINV), the physician needs to consider the emetogenicity of CTx agents, and other risk factors of CINV including female gender, young age, history of N/V with prior CTx cycles [20]. The most clinically relevant neurotransmitters involved in COVID-19-induced N/V are serotonin, substance P, and cholecystokinin, while CINV is mainly mediated by serotonin, dopamine, substance P, and cannabinoids [20, 23]. Considering almost common mediators, the management of N/V - in either case - is similar and includes the combination of a serotonin antagonist (*e.g.*, ondansetron) and a neurokinin inhibitor (*e.g.*, aprepitant) [20, 23].

The preceding information was intended to provide guidance and should not supersede clinical judgment. In case of suspicious findings in favor of COVID-19, both reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swab and chest computed tomography (CT) scan are recommended.

4. After the end of the chemotherapy course

- Minimize the modalities for response evaluation to decrease the patient's travel burden.

The following section will explore the specific recommendations provided by the experts of Shohada-e Tajrish Hospital to make a better decision for CTx of patients amidst the COVID-19 outbreak.

THE CONSENSUS FROM SHOHADA-E TAJRISH HOSPITAL FOR CTX AMIDST COVID-19 PANDEMIC

Herein, we have provided a step-by-step approach to CTx in cancer patients over the pandemic for better management of our patients. In conjunction with the preceding consideration, the flowchart presented in **Figure 1** is the current approach of the Clinical Oncologists of the Shohada-e Tajrish Hospital for the CTx of cancer patients during the pandemic. This approach is based on the national protocol for the management of cancer patients as well as the clinicians' experience [24].

https://doi.org/10.3947/ic.2020.52.4.496

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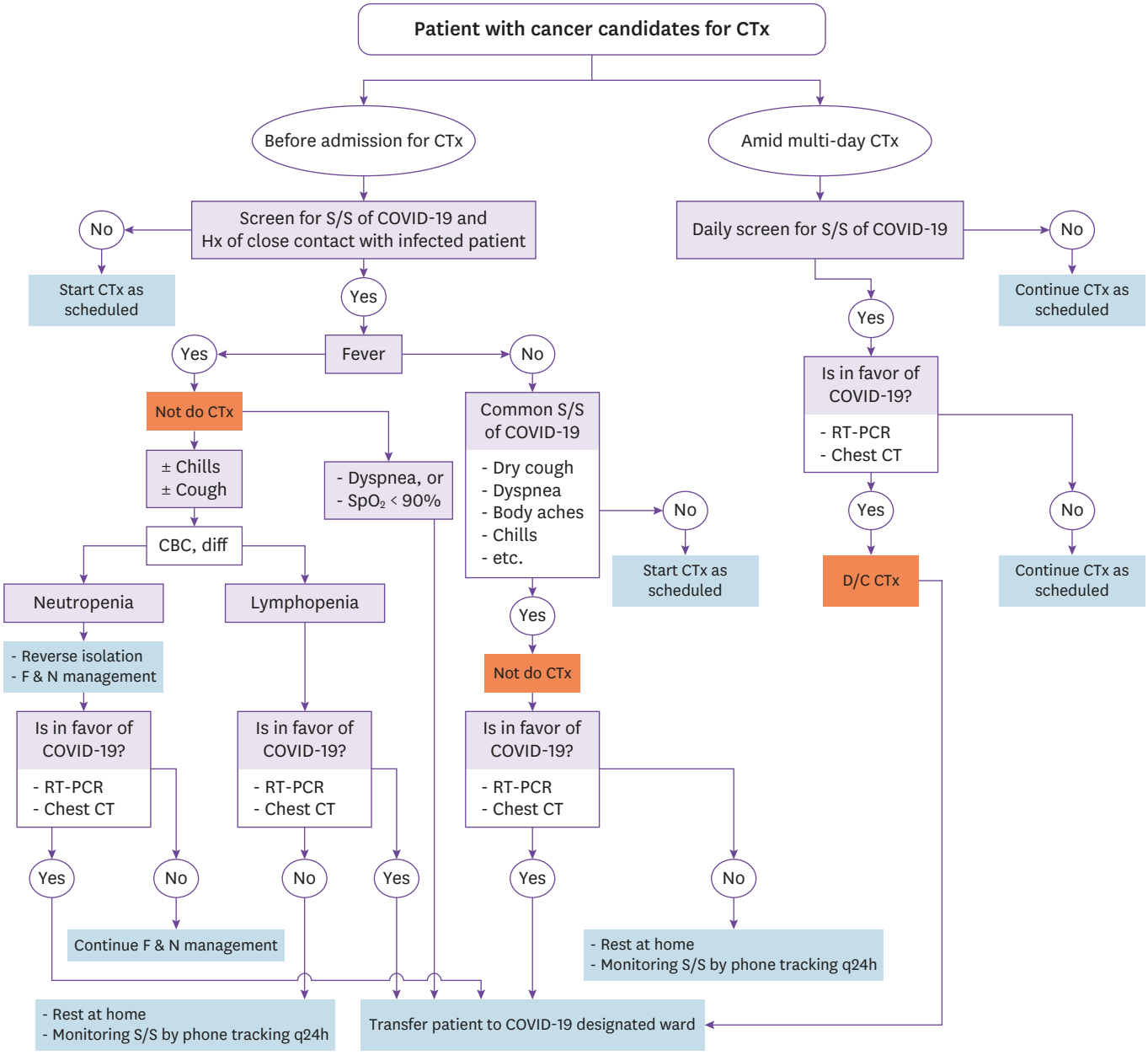

Figure 1. The consensus from the Shohada-e Tajrish Hospital for management of chemotherapy over COVID-19 pandemic.
COVID-19, coronavirus disease-2019; CTx, chemotherapy; S/S, signs and symptoms; CBC, diff, complete blood count with differential count; RT-PCR, reverse transcription polymerase chain reaction; CT, computed tomography; SpO_2, blood oxygenation saturation level; D/C, discontinue; F & N, fever and neutropenia; q24h, every 24-hours.

Before the onset of CTx, we evaluate the recent close contact with the infected individuals as well as common and typical S/S of COVID-19 (as mentioned above). If the patient passes the screening, CTx is done as per protocol. If not, he/she is categorized to 1) COVID-19 suspicious or 2) fever and neutropenia based on CBC and COVID-19-specific tests, including RT-PCR of nasopharyngeal swab and chest CT scan (**Fig. 1**). Due to limited medical facilities and a large number of patients referred for CTx, we have limited obtaining of PCR test and chest CT scan into 4 clinical conditions (**Fig. 1**).

https://doi.org/10.3947/ic.2020.52.4.496

In a specific clinical scenario of a patient who is a candidate for CTx (or radiotherapy) and has incidental radiographic findings - in favor of COVID-19 - on diagnostic (or simulation) chest CT, we consider it as a recovered finding and do treatment per planned with effective personnel protection. This recommendation is based on the findings of three cohort studies that clearly demonstrated no significant effect of recent anticancer therapies -including cytotoxic CTx and radiotherapy- on mortality of COVID-19 [10, 25, 26]. In our department, staff safety is a priority and PPE has been made available for all personnel in CT simulation and treatment of all patients during the viral pandemic.

In our center, for patients suspicious for COVID-19, we request both RT-PCR and chest CT scan for two reasons: 1) low sensitivity of RT-PCR and 2) low specificity of chest CT [27]. Of note, in patients with cancer, malignancy *per se* and CTx agents may further decrease the specificity of chest CT scan in detecting COVID-19. In patients who are receiving CTx, we check the S/S of COVID-19 every day, and in case of suspicious findings suspend the CTx and refer the patient to the designated COVID-19 ward.

Overall, the presence of each of the following findings causes a withdraw of CTx and patient's referral to the designated COVID-19 ward: 1) fever, 2) S/S of COVID-19, or 3) positive RT-PCR or chest CT in favor of COVID-19.

CONCLUSIONS

This article can provide a practical approach for our colleagues to manage patients with cancer who are candidates for CTx during the COVID-19 pandemic.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the personnel of the Clinical Oncology Department of Shohada-e Tajrish Hospital, Iran.

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