



Systemic Treatment of Cancer Patients during SARS-CoV-2 Pandemic

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Introduction

The SARS-CoV-2 pandemic has a significant influence on the functioning of every aspect of health care, including oncology. There is no doubt, the highest risk of complication or death due to SARS-CoV-2 infection is observed in elderly and patients with comorbidities [1]. Since the majority of cancers (>60%) is diagnosed in patients 65 years of age, cancer patients represent the population at high risk of COVID-19-related complications. Available literature data on the course of COVID-19 in cancer patients are scarce and comprise of two papers and 46 patients [2,3]. The clinical characteristics of COVID-19-infected cancer patients are largely unknown. PATIENTS AND METHODS In this retrospective cohort study, we included cancer patients with laboratory confirmed COVID-19 from three designated hospitals in Wuhan, China. The clinical data were collected from medical records from Jan 13, 2020, to Feb 26, 2020. Univariate and multivariate analyses were performed to assess the risk factors associated with severe events defined as a condition requiring admission to an intensive care unit, the use of mechanical ventilation, or death. RESULTS 28 COVID-19-infected cancer patients were included; 17 (60.7%). In the first publication, Liang et al. [2] evaluated data on 1590 COVID-19 patients, including 18 (1%) with a cancer diagnosis. The frequency of cancer in this population was 3-times higher than in the general Chinese population (0.29%). The majority of evaluated patients was in follow-up after cancer treatment, and systemic therapy was administered in only six patients. Four patients were diagnosed with lung cancer (2 receiving targeted treatment, 2 – chemotherapy), 1 with renal cell cancer (treated with immunotherapy), 1 with breast cancer (no information on the type of adjuvant treatment). Severe complications associated with COVID-19 were generally more frequent in cancer patients than in the general population (39% vs. 8%), but cancer patients were

older (mean age – 63.1 vs. 48.7) and smoked cigarettes (22% vs. 7%). In lung cancer patients, who had undergone chemotherapy or surgery within one month before COVID-19 diagnosis, severe complications were more frequent than in patients in a long-term follow-up - 75% vs. 43%, respectively.

In logistic regression model, the risk of severe complications due to COVID-19 was higher in patients with cancer history (OR = 5.39) than in patients with chronic obstructive pulmonary disease (OR = 3.39), diabetes (OR = 2,2) or arterial hypertension (OR = 1,87). In another publication, Zhang et al. [3] evaluated a population of 28 solid tumor patients (median age of 65 years) diagnosed with COVID-19 who were treated in three hospitals in Wuhan, China. The most frequent cancers were lung (25%), esophageal (14.3%), and breast (10.7%), and the majority of patients were diagnosed with localized (stage I-III) disease. All of the evaluated patients had a history of systemic treatment, and 21% had been treated systemically (11% - chemotherapy, 7% - targeted therapy, 4% radiotherapy, 4% immunotherapy) within 14 days of COVID-19 diagnosis. The majority of patients (71.4%) developed COVID-19 while staying at home. The most frequent symptoms were fever and cough (>80%). Severe COVID-19-related complications were observed in 70% of patients with metastatic disease and 44% of patients with stage I-III neoplastic disease. The mortality rate in the analyzed population (28.6%) was almost ten times higher than in general, Chinese population [4]. Multivariate analysis revealed that the risk of severe events was four times higher in patients receiving systemic treatment within 14-days of COVID-19 diagnosis (HR=4.079; 95%CI 1.086-15.322) [3].

Based on the relatively scarce literature data, it is hard to draw any definitive conclusion on the risk of COVID-19 in cancer

patients infected with SARS-CoV-2. It seems justified to assume that patients at high risk of severe complications associated with SARS-CoV-2 are those with advanced cancer during active systemic treatment. It is, however, challenging to determine what is the most critical factor – cancer localization, disease stage, or the type of systemic treatment. Liang et al. observed severe complications neither in a single breast cancer patient (52 years) nor 3 lung cancer patients (55 and 58 y.o. receiving targeted treatment; 47 y.o. receiving chemotherapy). On the other hand, severe complications were observed in a 63 y.o. lung cancer patient treated with palliative chemotherapy, and surprisingly, in a 58 y.o. RCC patient treated with immunotherapy [2].

The lack of robust data also prevents drawing of any conclusion regarding the optimal approach to cancer patients during the SARS-CoV-2 pandemics. However, there is no doubt that patients’ age, comorbidities, and type of cancer therapy may significantly increase the risk of severe complications and death due to COVID-19. Therefore, treatment strategy in cancer patients must be cautious and take into consideration not only patient performance status and comorbidities but also the goal of treatment (curative vs. palliative) and the necessity of immediate treatment (visceral crisis, severe symptoms).

Systemic treatment with Curative Intent

Treatment of patients with chemo curable cancers or cancers that can be cured by radio chemotherapy must be initiated without any delays and cannot be interrupted from any others than medical causes. In the case of neoadjuvant treatment, several aspects must be taken into consideration – the necessity of a particular type of treatment, the available treatment strategies, and the possibility of timely surgical treatment. In patients with locally advanced disease or in the case of neoadjuvant treatment with a significant impact on patients’ outcomes – neoadjuvant

therapy must be initiated immediately. Non-chemotherapy-based therapies, if justified (e.g., endocrine treatment in breast cancer), should be preferred. If local therapy (surgery, radiotherapy) is not available, the continuation of neoadjuvant treatment, beyond the standard number of cycles, should be considered (if no absolute contraindications are present).

In the majority of cases, adjuvant therapy may be postponed by more than 2 (in some patients even three months) following surgery. In patients with a high risk of disease recurrence (locally advanced disease, triple-negative breast cancer), adjuvant treatment should be initiated as soon as possible. Endocrine treatment (when possible) should be preferred over chemotherapy, especially in cancers with low Ki67 index or low grade (G1) [5].

Systemic treatment with Palliative Intent

Long-term interruption of palliative systemic treatment will ultimately lead to disease progression and possibly to patients’ death. Therefore, any decision on whether to withhold or postpone systemic treatment must take into consideration all consequences of potential disease progression, involving but not limited to the risk of organ failure, visceral crisis, severe symptoms, or sudden death. Since the duration and severity of the current epidemic crisis are unknown and patients’ access to cancer care may eventually become more restricted than presently, one should preferably optimize the systemic treatment strategies than just its withholding. One of the very convenient options in the current situation is the utilization of various metronomic chemotherapy strategies, which may act as a non-toxic, long-term maintenance treatment [6-8]. Recommended strategy of palliative treatment is described in table 1. Comprehensive treatment guidelines, along with recommended modification of chemotherapy regimens, have been described elsewhere [5].

Table 1: Strategy of palliative treatment.

Type of Systemic Treatment	Patients Characteristics	Treatment Modification
Chemotherapy	Complete response and/or long-lasting response	<ul style="list-style-type: none"> - maintenance chemotherapy (with metronomic regimens) - treatment holidays
	Asymptomatic, minimally symptomatic patients, with good disease, without risk of visceral crisis	<ul style="list-style-type: none"> - metronomic chemotherapy - decreased frequency of cycles - treatment holidays
	Requiring continuous systemic treatment (recently initiated therapy, risk of visceral crisis)	<ul style="list-style-type: none"> - cycles administered every 3/4-weeks – continuation - weekly cycles – modification to cycles administered every 3,4 weeks

Targeted Treatment	Receiving oral drugs with good tolerance	Continuation of therapy with decreased frequency of visits
	Receiving intravenous drugs	Continuation of therapy with up to 100% prolongation of time between cycles
Endocrine treatment		Continuation of treatment
Immunotherapy with check-point inhibitors	Complete response lasting for ≥ 24 months	Treatment cessation and observation
	Objective response lasting for ≥ 6 months	Continuation of therapy with up to 100% prolongation of time between cycles
	Recent initiation of treatment or disease stabilization or increasing response	Continuation of treatment

The current epidemic situation creates significant challenges both for oncologists and their patients. However, considering the available statistical and epidemiological data, the risk of death due to COVID-19 is several orders of magnitude lower than the risk of death of cancer patients deprived of proper cancer treatment. Now, more than ever, the oncologist must use their experience and skills in order to optimally treat their patients in the situation of limited human resources, restricted patient's mobility, and unknown duration of the pandemic. There is no doubt, the pandemic will end someday, and life will be back to „normal“. However, any avoidable disease recurrence or death of cancer patients due to the wrong decision will become an unnecessary tragedy to cancer patients and their families.

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