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RESEARCH

When to resume antitumor therapy in COVID-19-infected tumor patients: a retrospective, real-world study

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Abstract

Purpose To study the safety of resuming antitumor therapy in tumor patients infected with COVID-19.

Methods We collected the clinical information of patients with tumors who were infected with COVID-19 and resume antitumor therapy between December 2022 and June 2023. Information about antitumor therapy, COVID-19-related symptoms, laboratory tests, antitumor therapy-related adverse events (AEs), and re-infection with COVID-19 were recorded. Primary endpoints included the incidence of AEs and re-infection of COVID-19. The secondary endpoints included the incidence and duration of COVID-19 related symptoms.

Results The most common COVID-19 symptoms were fever (39.5%), cough (37.2%), and fatigue (44.2%). Most patients' symptoms lasted no more than a week Two patients were re-infected with COVID-19. All-grade AEs with an incidence rate > 10% included anemia, increased gamma-glutamyl transferase (GGT), anorexia, neutropenia, hypocalcemia, leukopenia, thrombocytopenia, increased alanine aminotransferase, increased aspartate aminotransferase, hypokalemia, hyponatremia, and nausea. Grade 3–4 AEs with an incidence rate higher than 5% included anemia, neutropenia, leukopenia, thrombocytopenia, anorexia, and vomiting. The incidence of AEs before and after COVID-19 infection did not show a significant difference.

Conclusion Resuming antitumor therapy early after SARS-CoV-2 test turned negative did not increase antitumor therapy-related AEs or the incidence of re-infection in COVID-19 infection patients.

Keywords COVID-19 · Tumor patients · Antitumor therapy · Safety · Reinfection

Introduction

Due to immune suppression caused by the tumor and antitumor therapy, tumor patients are at a higher risk of COVID-19 infection and higher prevalence of long COVD-19 [1, 2]. Tumor patients with COVID-19 also have a higher risk of treatment-related adverse events (AEs) and overall death owing to a variety of factors, including the presence of underlying disease, poor performance status, immunosuppression caused by the tumor, and antitumor therapy [3]. Patients with malignant tumors are nearly three times more likely to die from COVID-19 than the general population [4, 5]. Most antitumor therapies, especially cytotoxic drug therapy, cause immune suppression and prolong viral clearance in patients with tumor. Receiving chemotherapy before and after COVID-19 infection may exacerbate the severity of COVID-19 [1]. A recent report demonstrated that restart antitumor therapy 2–4 weeks after mild or moderate COVID-19 infection is safe [6]. According to National Comprehensive Cancer Network (NCCN) guideline, it is recommended that tumor patients hold antitumor therapy for at 10—20 days after infection with COVID-19, depending on disease severity [7, 8]. However, withholding antitumor therapy is an independent poor prognostic factor for tumor patients. Eligible patients should resume antitumor therapy as soon as possible [9]. However, there is no consensus as to when antitumor therapy should be

Xiaofen Pan and Mengyuan Zhu contributed equally to this work.

The study was approved by the Ethics Committee of the Seventh Affiliated Hospital, Sun Yat-sen University (Approval ID: KY-2023-080-01).

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restarted. In particular, it is questionable whether antitumor therapy should be suspended for such a long period of time, especially now that omicrons have become the predominant strain and overall pathogenicity has diminished.

Since December 2022, some tumor patients in our hospital have experienced COVID-19. In our clinical practice, we found that most tumor patients with COVID-19 are asymptomatic or only mildly ill. We attempted to resume antitumor therapy early after the patient's nucleic acid test was negative, and no exacerbation of COVID-19-related symptoms was observed. Therefore, we conducted this retrospective real-world study to collect the clinical information of tumor patients treated at our center who were infected with COVID-19 and received antitumor therapy between December 2022 and June 2023 to study the safety of resuming antitumor therapy in a short interval COVID-19 infected tumor patients.

Methods

Study design and patient inclusion

The current study was a retrospective analysis of patients with tumors and COVID-19 infection at our hospital between December 1, 2022, and June 30, 2023. The study was approved by the Ethics Committee of the XXX Hospital, XXX University (Approval ID: KY-2023–080-01).

The inclusion criteria were as follows: (1) patients with pathologically confirmed malignant tumors; (2) patients infected with COVID-19; (3) COVID-19 diagnosed by SAR-Cov-2 nucleic acid testing and/or antigen testing; and (4) tumor patients receiving systemic antitumor therapy if the SAR-Cov-2 nucleic acid test was negative.

The exclusion criteria were: (1) malignant tumors not confirmed by pathology, (2) COVID-19 not confirmed by nucleic acid or antigen testing, (3) tumor patients not receiving systemic antitumor therapy after COVID-19 infection, and (4) patients who died before SAR-Cov-2 nucleic acid testing was negative.

Antitumor therapy regimens

Patients received antitumor therapy as scheduled by their physicians. Antitumor therapy regimens include chemotherapy, targeted therapy, immunotherapy, or a combination of these therapies, depending on the tumor condition and the physician's choice.

Clinical information collection

The following information was recorded: (1) COVID-19-related symptoms, including fever, cough, fatigue, hyposmia/hypogeusia, stuffy nose, sore throat, conjunctivitis, myalgia, and diarrhea; (2) laboratory test results, including complete blood count (CBC), C-reactive protein (CRP), and procalcitonin; and (3) chest computed tomography (CT) abnormality. (4) SARS-CoV-2 nucleic acid/antigen test. (5) antitumor therapy (6) antitumor therapy related AEs.

End points

The primary endpoints included the incidence of AEs after antitumor therapy and re-infection with COVID-19, defined as re-positive nucleic acid or antigen tests within 28 days of the patient's antitumor therapy. The severity of AEs was recorded using CTCAE 5.0.

The secondary endpoints included the incidence and duration of COVID-19 related symptoms, changes in laboratory tests, and chest image examination.

Bias control and statistical analysis

In order to reduce recall bias and reporting bias, we used the information recorded in the medical record unless it was missing from the medical record.

Adverse events are graded according to common terminology criteria for adverse events version 5.0 (CTCAE 5.0).

The population for statistical analysis consisted of subjects who met the inclusion criteria but did not meet the exclusion criteria. Statistical descriptive analyses of the following parameters were conducted: (1) Baseline patient characteristics. (2) Incidence and duration of COVID-19 symptoms. (3) Laboratory tests and imaging abnormalities. (4) antitumor therapy types. (5) incidence of AEs. (6) Re-infection rate: defined as the incidence of nucleic acid/antigen tests re-positive within 28 days of the patient's antitumor therapy. Among the included patients, those who received antitumor therapy before the COVID-19 infection were set up as a self-control cohort. The incidence of AEs before and after COVID-19 infection was compared using a two-sided Fisher's exact test. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Between December 1, 2022, and June 30, 2023, there were a total of 989 hospitalizations at our center, of which 50

were infected with COVID-19. Of the patients infected with COVID-19, three were excluded because they died before the SARS-CoV-2 nucleic acid test was negative, and four were excluded because of incomplete information. Finally, 43 patients were included in the study (Figure S1). The median age of the patients was 60 years (range: 30–84 years). Nineteen (44.2%) patients were male. Thirteen (30.2%) patients received anti-COVID-19 therapy. The distribution of tumor type, clinical stage, and time interval between COVID-19 infection and previous antitumor therapy is shown in Table 1. Ten patients did not withhold antitumor therapy, among whom four received targeted therapy, two received targeted therapy + chemotherapy, three received targeted therapy + immunotherapy, and one received targeted therapy + immunotherapy + chemotherapy. Thirteen patients received antitumor therapy within 3 days after SARS-CoV-2 nucleic acid turned negative, seven received antitumor therapy 3–7 days after negative, and 10 received antitumor therapy more than one week after negative. Two patients received antitumor therapy without testing for COVID-19. Antitumor therapy regimens included chemotherapy (11.6%), targeted therapy(13.9%), immunotherapy (7.0%), immunotherapy + chemotherapy (16.3%), targeted therapy + chemotherapy (25.6%), immunotherapy + targeted therapy (11.6%), and immunotherapy + targeted therapy + chemotherapy(11.6%) (Table S1).

COVID-19 manifestation of cancer patients

The most common symptoms were fever (39.5%), cough (37.2%) and fatigue (44.2%). Other symptoms included hyposmia/hypogeusia (4.6%), stuffy nose (4.6%), sore throat (4.6%), myalgia (7.0%), and diarrhea (2.3%). Eleven patients (25.6%) were asymptomatic. Most of the patients' symptoms lasted no more than a week (Table 1).

Laboratory abnormalities with an incidence rate higher than 10% included lymphopenia (39.5%), decreased albumin level (32.5%), elevated C-reactive protein level (23.2%), elevated alanine aminotransferase level (13.9%), and thrombocytopenia (11.6%). Other laboratory test abnormalities included leukopenia (9.3%), elevated procalcitonin level (9.3%), elevated aspartate aminotransferase level (9.3%), neutropenia (4.6%), neutrophilia (2.3%), and thrombocytosis (7.0%) (Table 2).

The incidence of AEs after antitumor therapy

The patients were followed-up for 28 days after antitumor therapy. Two patients were reinfected with COVID-19. All-grade AEs with an incidence rate > 10% included anemia (58.1%), increased gamma-glutamyl transferase (GGT) (44.2%), anorexia (37.2%), neutropenia (27.9%), hypocalcemia (27.9%), leukopenia (23.2%), thrombocytopenia (20.9%), increased alanine aminotransferase (20.9%), increased aspartate aminotransferase (18.6%), hypokalemia (16.3%), hyponatremia (13.9%), and nause (13.9%). Other all grade AEs included vomiting (7.0%) and weight loss (4.6%). Grade 3–4 AEs with an incidence rate higher than 5% included anemia (16.3%), neutropenia(13.9%), leukopenia (9.3%), thrombocytopenia (7.0%), anorexia (7.0%), and vomiting (7.0%) (Table 3).

Table 1 Symptoms of COIVD-19 in tumor patients

Symptoms	$N=43$, n(%)
Fever	17(39.5)
Tmax (mean ± SD) (℃)	39.1 ± 0.6
Duration ≤ 3 days	10(23.2)
Duration 3–7 days	6(13.9)
Duration 7–14 days	1(2.3)
Duration ≥ 15 days	0(0)
Cough	16(37.2)
Duration ≤ 3 days	0(0)
Duration 3–7 days	13(30.2)
Duration 7–14 days	2(4.6)
Duration ≥ 15 days	1(2.3)
Fatigue	19(44.2)
Duration ≤ 3 days	4(9.3)
Duration 3–7 days	12(27.9)
Duration 7–14 days	2(4.6)
Duration ≥ 15 days	1(2.3)
Hyposmia/hypogeusia	2(4.6)
Duration ≤ 3 days	1(2.3)
Duration 3–7 days	0(0)
Duration 7–14 days	1(2.3)
Duration ≥ 15 days	0(0)
Stuffy nose	2(4.6)
Duration ≤ 3 days	1(2.3)
Duration 3–7 days	1(2.3)
Duration 7–14 days	0(0)
Duration ≥ 15 days	0(0)
Sore throat	2(4.6)
Duration ≤ 3 days	0(0)
Duration 3–7 days	0(0)
Duration 7–14 days	1(2.3)
Duration ≥ 15 days	1(2.3)
Myalgia	3(7.0)
Duration ≤ 3 days	3(7.0)
Duration 3–7 days	0(0)
Duration 7–14 days	0(0)
Duration ≥ 15 days	0(0)
Diarrhea	1(2.3)
Duration ≤ 3 days	1(2.3)
Duration 3–7 days	0(0)
Duration 7–14 days	0(0)
Duration ≥ 15 days	0(0)
Asymptomatic	11(25.6)

Table 2 Laboratory tests and imaging abnormalities in COVID-9-infected tumor patients

	$N=43$ $n(\%)$
Leukopenia	4(9.3)
Neutropenia	2(4.6)
Neutrophilia	1(2.3)
Lymphopenia	17(39.5)
Thrombopenia	5(11.6)
Thrombocytosis	3(7.0)
Elevated C-reactive protein	10(23.2)
Elevated procalcitonin	4(9.3)
Elevated alanine aminotransferase	6(13.9)
Elevated aspartate aminotransferase	4(9.3)
Decreased albumin	14(32.5)
Abnormal CT chest	7(16.3)

COVID-19 infection did not increased incidence of AEs

Among the 43 included patients, 38 had a history of antitumor therapy before they were infected with COVID-19. We used these patients as a self-control cohort and reviewed their AEs experienced by these patients before they were infected with COVID-19. The incidence of AEs before and after COVID-19 infection was compared. The results showed that the incidence rates of increased alanine aminotransferase (26.3% vs. 20.9%, $p=0.0003$) and aspartate aminotransferase (28.9% vs. 18.6%, $p<0.0001$) were higher before they were infected with COVID-19. No significant differences were observed in the incidence rates of other AEs (Table 3). We further performed a pair comparison in the 38 patients who had a history of antitumor therapy before and after COVID-19 infection. The incidence of AEs before and after COVID-19 did not show a significant difference (Fig. 1).

We further characterized the incidence of AEs in patients with different time intervals between antitumor therapy and negative SAR-Cov-2 nucleic acid test results. No differential trend was observed in the incidence of AEs among the patients with different time intervals (Table 4), although the sample size was too small to perform statistical analysis.

Discussion

Although the NCCN guideline recommends withholding antitumor therapy for 10–20 days in tumor patients infected with COVID-19 [8], there is not much evidence-based

Table 3 Adverse events after the first cycle antitumor therapy after COVID-19 infection

Adverse events	Received antitumor therapy after COVID-19 infection, $N=43$			Received antitumor therapy before COVID-19 infection, $N=38$			p-value[§]
	Grade 1–2 $n(\%)$	Grade 3–4 $n(\%)$	All grade $n(\%)$	Grade 1–2 $n(\%)$	Grade 3–4 $n(\%)$	All grade $n(\%)$	
Leukopenia	6(13.9)	4(9.3)	10(23.2)	3(7.9)	4(10.5)	7(18.4)	> 0.05
Neutropenia	6(13.9)	6(13.9)	12(27.9)	3(7.9)	4(10.5)	7(18.4)	> 0.05
Anemia	18(41.9)	7(16.3)	25(58.1)	14(36.8)	7(18.4)	21(55.3)	> 0.05
Thrombopenia	6(13.9)	3(7.0)	9(20.9)	5(13.1`)	4(10.5)	9(23.7)	> 0.05
Alanine aminotransferase increased	9(20.9)	0(0)	9(20.9)	8(21.0)	2(5.3)	10(26.3)	***0.0003***
Aspartate aminotransferase increased	8(18.6)	0(0)	8(18.6)	9(23.7)	2(5.3)	11(28.9)	***< 0.0001***
GGT increased [†]	17(39.5)	2(4.6)	19(44.2)	14(36.8)	3(7.9)	17(44.7)	> 0.05
Hypocalcemia	12(27.9)	0(0)	12(27.9)	14(36.8)	0(0)	14(36.8)	> 0.05
Hypokalemia	7(16.3)	0(0)	7(16.3)	8(21.0)	1(2.6)	9(23.7)	> 0.05
Hyponatremia	6(13.9)	0(0)	6(13.9)	8(21.0)	0(0)	8(21.0)	> 0.05
Anorexia	13(30.2)	3(7.0)	16(37.2)	12(31.6)	2(5.3)	14(36.8)	> 0.05
Nause	4(9.3)	2(4.6)	6(13.9)	3(7.9)	2(5.3)	5(13.1`)	> 0.05
Vomiting	0(0)	3(7.0)	3(7.0)	2(5.3)	1(2.6)	3(7.9)	> 0.05
Weight loss	2(4.6)	0(0)	2(4.6)	1(2.6)	0(0)	0(0)	> 0.05
Re-positive for COVID-19 test[‡] in 28 days	-	-	2(4.6)	-	-	-	-

[†]GGT, gamma-glutamyl transferase

[‡] Positive for antigens or nucleic acids

[§] Comparison of incidence rates of AEs of all grade AEs. Two-sided Fisher's exact test

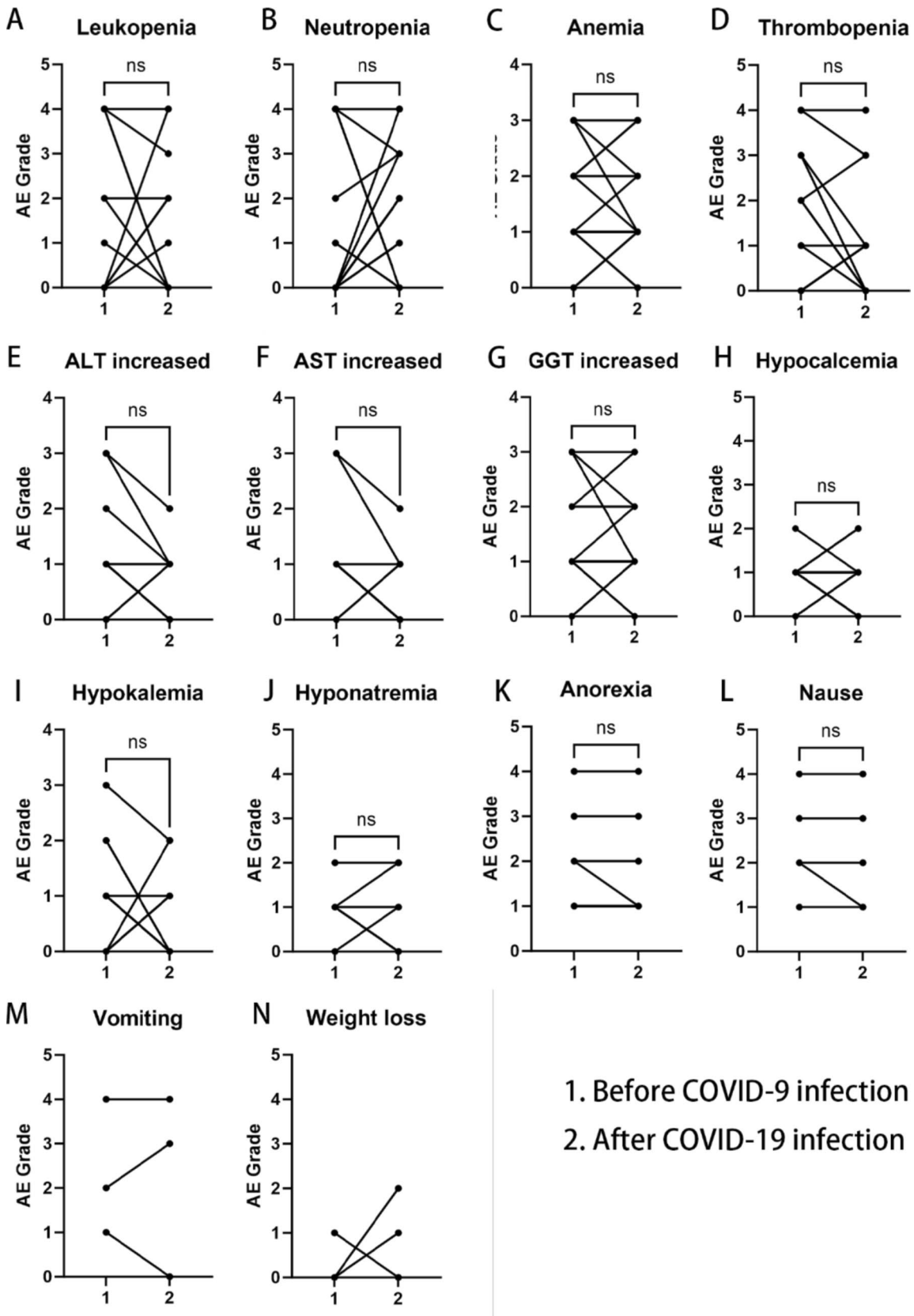
information about when antitumor therapy can be resumed in these patients, especially now that the low toxicity and highly transmissible omicron has become the dominant strain.

In the current study, we retrospectively collected clinical information from tumor patients with COVID-19 who were treated at our center between December 2022 and June 2023 to analyze the safety of resuming antitumor therapy early after SARS-CoV-2 nucleic acid tests turned negative. Most of the patients received antitumor therapy within 7 days after the SARS-CoV-2 nucleic acid test turned negative, and about half of the patients received antitumor therapy within 3 days. None of the patients died of antitumor therapy related AEs. The incidence of grade 3–4 AEs was acceptable. To better study the impact of COVID-19 infection on the safety of antitumor therapy, we selected patients who had received antitumor therapy prior to infection with COVID-19 from the current cohort as a self-control cohort and compared the incidence of AEs between the two cohorts. The results showed that antitumor therapy after experiencing COVID-19 infection did not increase the incidence or severity of AEs compared to receiving antitumor therapy before COVID-19 infection. However, our study showed that the incidence rates of increased alanine aminotransferase (26.3% vs. 20.9%, $p = 0.0003$) and aspartate aminotransferase (28.9% vs. 18.6%, $p < 0.0001$) were higher before they were infected with COVID-19. Nevertheless, the paired comparison of the same patient before and after COVID-19 infection did not show a statistical difference. This may be due to the small sample size.

Previous studies have reported that antitumor therapy, especially chemotherapy, causes immune deficiencies in patients with malignant tumors, resulting in prolonged clearance of replication-competent viruses (> 20 days) [10]. Patients who received chemotherapy within one month of COVID-19 infection had a higher risk of clinically serious events than those who did not receive chemotherapy [1]. Therefore, the NCCN guideline recommends that oncology patients with COVID-19 withhold antitumor treatment for 10–20 days, depending on the patient's severity and subsequent antitumor regimens. A previous study indicated that restart antitumor therapy in breast cancer patients 2–4 weeks after mild or moderate COVID-19 infection did not increased treatment-related adverse events [6]. However, in the current study, most tumor patients received antitumor therapy within a week, and half of the patients received antitumor therapy within 3 days after SARS-CoV-2 turned negative, and the incidence or severity of AEs did not increase. It should be pointed out that 23.2% of the patients in our study did not hold antitumor therapy when they were infected, and no increased incidence of AEs was observed in these patients. Among these patients, four received targeted therapy, two received targeted therapy + chemotherapy, three received targeted therapy + immunotherapy, and one received targeted therapy + immunotherapy + chemotherapy. Based on this, we questioned whether it is necessary to withhold antitumor therapy during the period when omicrons are the predominant strains, especially in patients receiving only targeted therapy and immunotherapy rather than chemotherapy.

In addition to antitumor therapy-related AEs, another issue of concern is whether resuming antitumor therapy shortly after SARS-CoV-2 turned negative can cause COVID-19 re-infection because immunity would be impaired by antitumor therapy. In this study, re-infection with COVID-19 only occurred in two patients. A previous study reported that re-positive COVID-19 tests occurred in 2.4%–69.2% of recovered COVID-19 patients[11]. The inconsistency between our results and previous reports may be due to the fact that omicron had became the predominant strain at the time of data collection for this study, and it is highly likely that most of the included patients were infected with omicron, which is highly infectious but has less toxicity than any previous strains.

In addition to antitumor therapy-related AEs, we recorded the clinical manifestations of COVID-19 in tumor patients. We found that most of our patients had mild infections, and approximately one-fourth of them were asymptomatic. Most of the patients' symptoms relieved within a week. The results are inconsistent with previous reports that oncology patients are more likely to develop severe infections [1, 12]. Interestingly, we noticed that the clinical manifestations of the non-tumor population (physicians and nurses) infected with COVID-19 in the same period in the same ward were more symptomatic. The main symptoms included high fever, sore throat, muscle aches, headache, loss of appetite, and diarrhea, and the duration of symptoms was longer [13]. This suggests that mild symptoms in tumor patients may be associated with a different immune response to the SARS-CoV-2 strain between tumor patients and non-tumor individuals, rather than the low toxicity of the strain. The severity of COVID-19 may be related to the immune response of the body to the virus [14]. Previous studies have indicated that individuals with severe COVID-19 have higher levels of neutralizing antibodies than those with mild disease or asymptomatic infections [15, 16]. Patients with tumors have impaired immune function to some extent, and may have a weaker immune response to viruses, producing lower levels of antibodies and a weaker inflammatory response, resulting in milder symptoms [17, 18]. However, mild symptoms do not mean mild disease. Impaired immune function may lead to decreased viral clearance and prolonged viral clearance time, thus increasing the risk of transition to severe disease [10]. Therefore, we propose that in patients with tumors or other immunocompromised populations, immunity should


A Leukopenia
B Neutropenia
C Anemia
D Thrombopenia
E ALT increased
F AST increased
G GGT increased
H Hypocalcemia
I Hypokalemia
J Hyponatremia
K Anorexia
L Nause
M Vomiting
N Weight loss
AE Grade
ns
1. Before COVID-9 infection
2. After COVID-19 infection

◂**Fig. 1** The pair comparison in the patients who had antitumor therapy history before and after they were infected with COVID-19. (**A**) leukopenia (**B**) neutropenia (**C**) anemia (**D**) thrombopenia (**E**) alanine aminotransferase (ALT) increased (**F**) aspartate aminotransferase (AST) increased. (**G**) gamma-glutamyltransferase (GGT) increased (**H**) hypocalcemia (**I**) hypokalemia (**J**) hyponatremia (**K**) anorexia (**L**) nausea (**M**) vomiting (**N**) weight. ns, non-significant. For vomiting and weight loss, the incidence rate was too low to compare

be increased after infection with COVID-19 to shorten the time to viral clearance. However, in individuals with severe COVID-19 (not with tumors or other infections), appropriate suppression of immune function may be helpful in reducing symptoms after the clearance of the virus (negative nucleic acid test).

In this study, a retrospective analysis of COVID-19-infected tumor patients found that resuming antitumor therapy shortly after nucleic acid tests turned negative did not increase antitumor therapy-related AEs or the incidence of COVID-19 re-infection. Resuming antitumor therapy early after SARS-CoV-2 test turned negative may be safe. In addition, we suggest that in immune-compromised populations, immunity should be strengthened during COVID-9 infection to shorten the time to viral clearance, and in immune-competent populations, appropriate suppression of immune function after viral clearance may help reduce symptoms. However, some limitations of this study should be noted. First, this study was a retrospective analysis and may have had some recall bias. Second, the patients included in this study were all from the same center, and the clinical presentation may have been influenced by the prevalent strains in the region and differed from those in other regions. Finally, the sample size of this study was small, and more prospective clinical studies are needed to validate the results of this study further.

Conclusion

Resuming antitumor therapy early after SARS-CoV-2 turned negative did not increase antitumor therapy-related AEs or the incidence of re-infection in COVID-19 infection patients.

Table 4 All-grade adverse events for patients with different time interval between antitumor therapy and SAR-Cov-2 nucleic acid test negative

Adverse events	0 day ($N=10$) n(%)	1–3 days ($N=13$) n(%)	3–7 days ($N=7$) n(%)	≥8 days ($N=10$) n(%)
Leukopenia	2(20.0%)	4(30.8%)	0(0%)	3(30.0%)
Neutropenia	1(10.0%)	5(38.5%)	1(14.3%)	4(40.0%)
Anemia	6(60.0%)	10(76.9%)	2(28.6%)	6(60%)
Thrombopenia	2(20.0%)	1(7.7%)	2(28.6%)	4(40.0%)
Alanine aminotransferase increased	2(20.0%)	3(23.1%)	0(0%)	3(30.0%)
Aspartate aminotransferase increased	1(10.0%)	2(15.4%)	0(0%)	4(40.0%)
GGT increased [†]	6(60.0%)	5(38.5%)	1(14.3%)	7(70.0%)
Hypocalcemia	2(20.0%)	6(46.2%)	1(14.3%)	3(30.0%)
Hypokalemia	1(10.0%)	3(23.1%)	0(0%)	2(20.0%)
Hyponatremia	2(20.0%)	2(15.4%)	0(0%)	2(20.0%)
Anorexia	4(40.0%)	6(46.2%)	0(0%)	4(40.0%)
Nause	1(10.0%)	2(15.4%)	0(0%)	1(10.0%)
Vomiting	1(10.0%)	0(0%)	1(14.3%)	0(0%)
Weight loss	1(10.0%)	0(0%)	0(0%)	1(10.0%)
Re-infection of COVID-19 within 28 days	1(10.0%)	1(7.7%)	0(0%)	0(0%)

[†]GGT, gamma-glutamyl transferase

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Author contributions XP, MZ, GH, XL, JL, SH, and BW had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. XP, MZ and BW wrote the manuscript. GH,XL, JL and SH prepared the tables and figures. XP, MZ, GH, XL, JL, SH, and BW have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

Ethical compliance All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Seventh Affiliated Hospital, Sun Yat-sen University (Approval ID: KY-2023–080-01).

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