Infectious Agents and Cancer

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Clinical impact of concurrent autologous adoptive T cells immunotherapy in active COVID-19 infected cancer patients for chemotherapy

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Abstract

Background The concurrent presence of COVID-19 infection in advanced cancer patients has increased the mortality since the compromised immunity was inevitably worsen. The role and clinical impact of autologous adoptive T cell immunotherapy (ACT) designed for anti-cancer treatment were not known in such circumstances. The safety and potential immune reconstitution of concurrent ACT in advanced cancer patients with active COVID-19 infection have yet unknown as well. The effect of infused ACT on the symptom severity manifestation should be summarized.

Methods In this respectively clinical observation study, patients were non-randomized enrolled from the two centers according to the regular therapeutic plans including stage IV cancer patients for scheduled ACT, chemotherapy, cancer patients with symptomatic COVID-19 but without ACT, neither cancer or non-ACT but symptomatic cases of COVID-19 infection. We have incorporated the age-adjusted Charlson comorbidity index (aCCI) for each patient to compare the prognosis of the three groups. All patients were planned for the scheduled standard anti-cancer therapeutic considerations, chemotherapy plus ACT as planned as well as the supportive care.The clinical efficacy and impact of ACT on cancer patients within the 3 months from the peripheral blood apheresis, dendritic cell (DC) and cytokine induced killer T cell (CIK-T) infusion and subsequent co-existence of COVID-19 infection were recorded as the primary objective. During the same period, the cancer cases without ACT and others were collected to compare the occurrence of both severe and death rate respectively.

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Results There were 123 patients (35 of ACT, 23 of non-ACT, 65 of non-cancer) with similar aCCI. There were similar cohort-level COVID-19 in-hospital case fatality rates consistent with previously reported data for non-cancer (26.2%, 17/65) and non-ACT cancer (52.2%, 12/23) among those admitted severe cases after the adjustment.There were little overlapped adverse reactions during the ACT therapeutic period even in the presence of active COVID-19 infection. No death case was occurred (0/35) when those exposed to ACT regimen. Cancer patients receiving ACT had a shorter mean time to alleviation of symptoms compared with non-ACT and non-cancer (4.46 versus 16.88 and 17.90 days respectively) as well as the lowered severity incidence of symptoms ($P=0.0010$). The infused ACT has not significant impact on peripheral blood count whereas the amount of $CD3^{-}CD16^{+}CD56^{+}$ NK cells increased ($P=0.0017$). The quantity of infused ACT was favorable for augmentation of possibility of severe to mild symptom shift.

Conclusions These data demonstrate the clinical safety profiles while ACT infusions with active COVID-19 infection.The intervention of ACT for cancer patients could generate the benefit for symptom alleviation with improved recovery time. The concurrent ACT for advanced cancer patients during such infectious pandemic might simultaneously leverage and reduce the risk of immune compromised situation for subsequent chemotherapy complications.

Keywords Autologous adoptive cellular immunotherapy, COVID-19 infection, Safety.

Background

The attention for COVID-19 infection linked to various diseases has been extensively reported in the past three years to address the different complications. There are adequate data to demonstrate the death rate in the different affected population [1, 2]. Cancer patients were more vulnerable to COVID-19. A large multi center clinical study collecting 105 hospitalized patients with cancer and 536 patients without cancer. Those showed that patients metastatic cancer (stage IV) had the highest frequency of severe events. These evidence-based clinical studies have showed that patients with immune compromised and or cellular immunity impairment were inclined to severe clinical outcome [3]. The variation of infection severity between cancer types might provide the insights for understanding the critical roles of T cell immunity [4]. T cell immunity impairment of cancer patients could be calamitous when concomitant with COVID-19 infection [5–7]. The cancer patients were more popularized featured by T cell exhausting and immunity slumping [8, 9].

We have been studying adoptive T cell therapy (ACT) as an anticancer therapy in advanced tumors for more than 30 years Our protocols have been evolved from combination of ACT with standard chemotherapy to immune reconstruction and T cell immunity impairment restoration [10–17]. These autologous cellular products are generated from apheresis by culturing peripheral blood mononuclear cells in a cytokine cocktail (including rhIFN-γ, OKT-3, rhIL-2 and IL-1α). Following an infusion of these cells, peripheral blood cytotoxic T cells and unique T cell receptor (TCR) clones restore and suppressive T cell populations decrease [18].

During the COVID pandemic, cancer patients who were scheduled for standard chemotherapy had risk exposure for both cancer progression and concurrent COVID-19 infection to trigger the secondary immune impairment attack.In this unprecedented period, we had the opportunity to study the safety and potential immunological effects of ACT on COVID-19 infection. In this study, we retrospectively collected data during the surge in COVID-19 infection from November 2022 to February 2023 in China. We had investigated the safety when such infected cancer patients were on schedule to receive the ACT and non-randomized selected two controls groups that those without ACT and solo infected population admitted from two hospitals from Beijing and Shanghai cities.Those two homogeneous cancer patient services were manageable with the same group physicians. They have employed the similar clinical protocols for ACT and chemotherapy. It was essential to observe the clinical efficacy and impact of ACT on COVID-19 severity and mortality in three groups of patients. More detail included those receiving ACT as part of their cancer therapy (Department of Medical Oncology, Fudan University Pudong Medical Center, Shanghai, China), those not receiving ACT for cancer therapy, and non-cancer patients admitted with COVID-19 (Department of Oncology of Beijing Zhongguancun Hospital, Chinese Academy of Sciences, Beijing). As those two sites were integrated in cancer treatment with the same protocols to manage the admitted cancer patients to avoid the therapeutic bias and data discrepancy. The both non-ACT COVID-19 infected cases were not randomized selected.

The objective of this work was to study retrospectively the clinical efficacy and safety effect of ACT on cancer patients concurrent administered by conventional anti-cancer treatment.The secondary purpose included the potential immunologic effect of ACT on mortality and severity of COVID-19 in cancer patients. All patients has been consent with the documentation.The ACT cell transfusion of this study was approved by the Medical Ethics Committee of Fudan University Pudong

Medical Center, Shanghai, China, Ethics number: 2021-IIT-021-E02.

Methods

Patient and symptom assessment

The inclusion criteria for this retrospective study were: Cancer patient being treated with ACT, cancer patient not receiving ACT, and patients without cancer and admitted with COVID-19 infection. Data collected from hospital records included patient age, gender, relevant medical history, diagnosis of COVID-19, symptom location and duration of diagnosis and treatment process, and ACT based infusion (dose, schedule, and treatment cycle). The admitted patients were classified severe according to NIH criteria infected by COVID-19, including either of following symptoms, shorten breath frequency above 30 per minute, SPO_2 less than 94%, the ratio of PaO_2 to FiO_2 less than 300 mmHg or lung infiltration area above 50% according to COVID-19 treatment guidelines, which released by National Institutes of Health.

Time until alleviation of symptoms was defined as the time from diagnosis of COVID-19 until the chart indicated that the patient's symptoms had resolved predominantly represented by respiratory symptoms. A Charlson comorbidity index (aCCI) score was calculated for all patients (Table 1).

Comorbidities at COVID-19 diagnosis

For the comparison of comorbidities at COVID-19 diagnosis upon the cancer with ACT group, according to the published literature, we have referred the inclusion of chronic obstructive pulmonary disease (COPD), hypertension (HTN), congestive heart failure (CHF), diabetes mellitus (DM), chronic kidney disease (CKD), liver cirrhosis (HC), cerebral infarction (CI). Those parameter could deteriorate the outcomes and severity of COVID-19 (Fig. 1).

Preparation of ACT products

Generation of DC/CIK-T cells

CIK-T cell was prepared as described in our previous studies [16]. Briefly, mononuclear cells were harvested from peripheral blood and expanded in vitro. For the induction of DC/CIK-T cells, mobilization of PBMC was performed with GM-CSF 5 mcg/kg sq per body weight (Kirin Pharm Co. Ltd.) to patient until the level of mono nuclear cells reached 1.5×10^9/L. Then, PBMCs were separated by a COBE Spectra cell separator (Terumo, United States).The each apheresis was performed from a total of circulating blood volume of 8000 ml to harvest 80–90 ml PBMC.The 25 ml of fresh apheresis product was co- cultured for 7 d with IL-4 (1,000 U/mL; R&D Systems, Inc.), TNF-a (20 ng/mL; R&D Systems, Inc.) and GM-CSF (800 U/mL; Amoytop Biotech Co., Ltd.) in vitro to generate autologous DCs. Mononuclear cells were separated by gradient centrifuge and activated in vitro with the recombinant cytokines IL-2 at 1,000 U/mL (Boehringer Mannheim, Germany), IFNgamma at 1,000 U/mL (Boehringer Mannheim, Germany) and CD3 antibody at 1.7 mL/mL (Boehringer Mannheim, Germany) for 7 to 10 days. The phenotypes of DCs (CD80, CD86, HLA-DR, CD1a, and CD11c) and CIK-T cell (CD3 and CD56) were characterized by flow cytometry. The proportion of CD80 plus CD86 cells reached greater than 80% among the cultured cells in the autologous DC-specific cultures. The cultured autologous DCs were then mixed with cultured CIK-T cellat a proportion of 1:100, and then DC/CIK-T cellwere harvested for intravenous administration to patient. The repetitive saline washing was employed to remove those cytokines before the DC/CIK-T cell harvest.The three separate bags of hemispheres were frozen at -80℃ for consecutive thawing and induction.One operation of hemispheres could offer 4 cycles of ACT. The infused ACT amount was calculated for those cancer patients (Table 2).

Lymphocyte subpopulation analysis

Lymphocyte subpopulation analysis was conducted as described earlier [19], using Beckman Coulter's CYTO-STAT tetrachrome CD45-FITC/CD4-RD1/CD8-CD/CD3-PC5 and CYTO-STAT tetrachrome CD45-FITC/CD56-RD1/CD19-ECD/CD3-PC5 to stain blood samples. The percentages of CD4 + and CD8 + T lymphocytes, as well as CD56 + NK and CD19 + B cells were measured using the flow cytometry system (Beckman Coulter).

Statistical analysis

Descriptive statistics were used for clinical characteristics. Overall survival was estimated using the Kaplan–Meier method, considering death due to any cause as an event and time from COVID-19 infection to the last date of follow-up as survival time.Univariate and multivariate risk factor analyses for overall survival were performed using the Cox regression model. Statistical analyses were performed using GraphPad Prism 8.0.2 and Origin 2023. Group sizes and definition of error bars were indicated in figure legends. Statistical analysis was performed using two-tailed Student's t test (comparison between two groups) or one-way analysis of variance (ANOVA; comparison among more than two groups). $P < 0.05$ was considered significant; significant values were indicated as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

Table 1 Patient demographic with clinical data and outcomes

Patients information	Number of patients, *n* (%)		
	Cancer patients with ACT	Cancer patients without ACT	Admitted patients
Number of infected persons	35	23	65
Age			
15-49Y	8 (22.9%)	0 (0.0%)	0 (0.0%)
50-64Y	13 (37.1%)	1 (4.3%)	2 (3.1%)
≥ 65Y	14 (40.0%)	22 (95.7%)	63 (96.9)
Gender			
Male	16 (45.7%)	12 (52.2%)	35 (53.8%)
Female	19 (54.3%)	11 (47.8%)	30 (46.2%)
Smoking history			
Non-smoker	18 (51.4%)	9 (39.1%)	32 (49.2%)
Ex-smoker	2 (5.7%)	3 (13.1%)	5 (7.7%)
Active-smoker	15 (42.9%)	11 (47.8%)	28 (43.1%)
COVID-19 vaccination status*			
Yes	9 (25.7%)	4 (17.4%)	14 (21.5%)
No	26 (74.3%)	19 (82.6%)	51 (78.5%)
Comorbidities			
COPD	4	7	23
HTN	28	19	36
CHF	2	1	6
DM	17	10	22
CKD	1	0	3
HC	3	2	4
CI	4	3	10
aCCI**	5.49	6.13	5.24
Number of severe cases	4 (11.4%)	23 (100.0%)	48 (73.8%)
Severe symptoms			
Pneumonia	4	23	48
Liver function insufficiency	0	3	2
Cardiovascular & cerebrovascular diseases	0	1	4
Renal function impairment	0	1	2
Rash	0	0	1
Diarrhea	0	0	2
Thrombocytopenia	0	0	1
Thrombosis	0	0	0
Clinical outcomes			
Number of death	0 (0%)	12 (52.2%)	17 (26.2%)
Mean time to symptomatic. alleviation (Days)	4.46	17.90	16.88
Changes of lymphocytes and neutrophils before and after infection ($10^{\wedge 9}$/L) (Mean pre -and post treatment)			
Neutrophils	5.443/4.225	6.224/5.321	9.439/6.435
Lymphocytes	1.224/1.237	1.346/1.358	1.201/1.390

* There were no differences of vaccinations frequency in those cancer with ACT versus cancer without ACT ($P = 0.6495$)

**we have referred the age Charlson comorbidity index (aCCI) [1]score associated with death in COVID-19 patients hospitalized to create the current scores in cancer patients

The main methods for calculating aCCI

16 common diseases are listed and divided into 4 categories according to the severity of the disease, which are scored 1, 2, 3 or 6 points

COPD, chronic obstructive pulmonary disease; HTN, hypertension; CHF, congestive heart failure; DM, diabetes mellitus; CKD, chronic kidney disease; HC, liver cirrhosis; CI, cerebral infarction

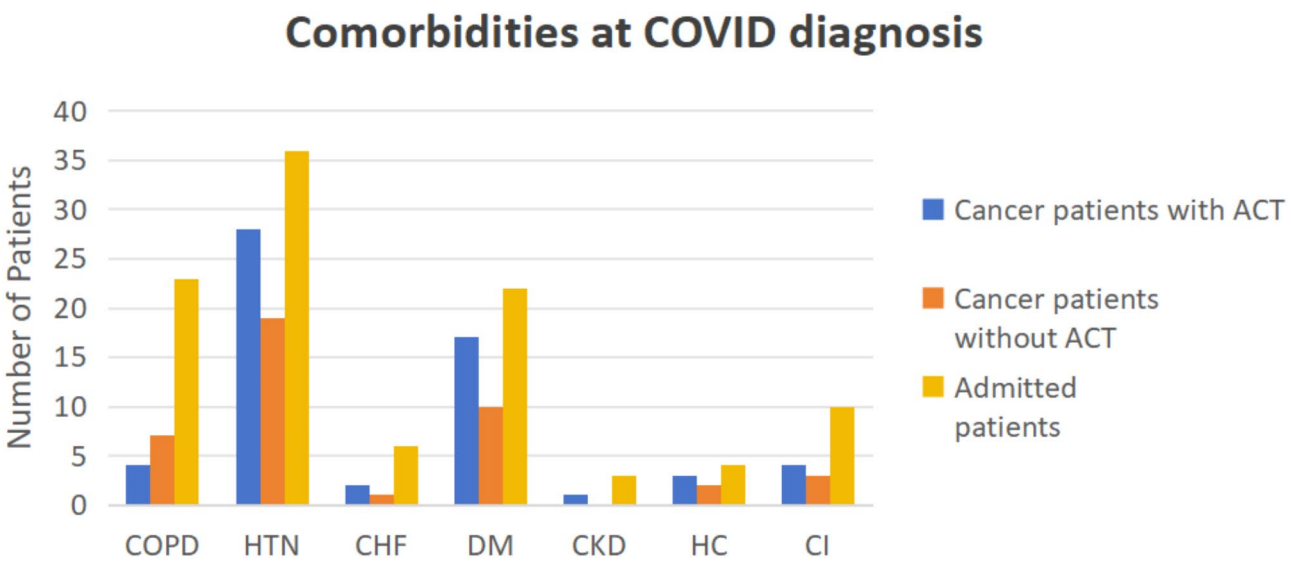

Fig. 1 Comorbidities at COVID diagnosis. The accumulative case for comorbidities at COVID diagnosis. COPD: chronic obstructive pulmonary disease; HTN: hypertension; CHF: chronic heart failure; DM: diabetes mellitus; CKD: chronic kidney disease; HC: hepatic cirrhosis; CI: cerebral infarction

Table 2 Specifications of CIKs infusions in COVID-19 infected cancer patients with ACT

Advanced Cancer types	Case	Number of ACT cycles	Total number of ACT infused	Number of severe cases
lung	5	14	39.13×10^9	0
ovarian	5	13	39.02×10^9	1
colon -rectal	4	11	31.46×10^9	1
breast	3	7	20.65×10^9	0
gastric	3	7	21.98×10^9	0
pancreatic	2	4	12.8×10^9	0
kidney	2	7	20.76×10^9	0
laryngocarcinoma	2	4	11.98×10^9	1
hepatobiliary	2	6	17.88×10^9	0
liver	2	5	15.25×10^9	0
bladder	1	1	3.02×10^9	0
cervical	1	2	6.01×10^9	0
nasopharynx	1	3	8.91×10^9	0
esophagus	1	3	8.89×10^9	1
sarcoma	1	2	6.22×10^9	0

Results

Clinical outcome from the different groups

This retrospective study included 123 patients infected with COVID-19 who were admitted to one of two hospitals in Shanghai and Beijing from November 1 to December 31, 2022. The group was divided by whether they were cancer patients before COVID-19 infection and among the cancer patients, whether they had received ACT treatment. This resulted in three groups: 35 patients in the ACT-treated cancer patient group, 23 patients in the non-ACT cancer patient group, and 65 patients in the non-cancer group. Demographics are in Table 1. 9 (25.7%), 4 (17.4%), and 14 (21.5%) had been previously vaccinated at least once with a COVID-19 vaccine, respectively. Only 4 people (11.4%) in the ACT cancer patients' group were classified as severe cases manifested by pulmonary symptoms. In the cancer patients without ACT group, 23 patients (100%) were severe, and 48 patients (73.8%) were severe in the Non-cancer patients' group. In addition to respiratory symptoms, complication symptoms also included liver dysfunction, cardio cerebral vascular disease, renal function damage, rash, diarrhea, thrombocytopenia and other symptoms were recorded. There was no death in the ACT cancer patients group, 12 deaths in the cancer without ACT patients group (52.2%), and 17 deaths in the Non-cancer patients group (26.2%).

Overall prevalence of ACT patients' distributions and severity of COVID-19 infections

Sankey analysis was used to analyze the infection of COVID-19 pneumonia in tumor patients who received ACT before the outbreak of COVID-19 during the surging period of COVID-19 pneumonia and the symptoms after infection. We found that most of the cancer patients with ACT infected with COVID-19 had moderate symptoms, and only a few had severe symptoms (Fig. 2a). We did not find a correlation between severity of symptoms and number of ACT infusions within the ACT group (Fig. 2b). Time until alleviation of symptoms was also substantially shorter in the ACT group (4.46 days) compared with the cancer patients without ACT group and the non-cancer patients' group (17.90 and 16.88 days respectively ($p<0.0005$ for the comparison of ACT versus non-ACT cancer patients) (Fig. 3).

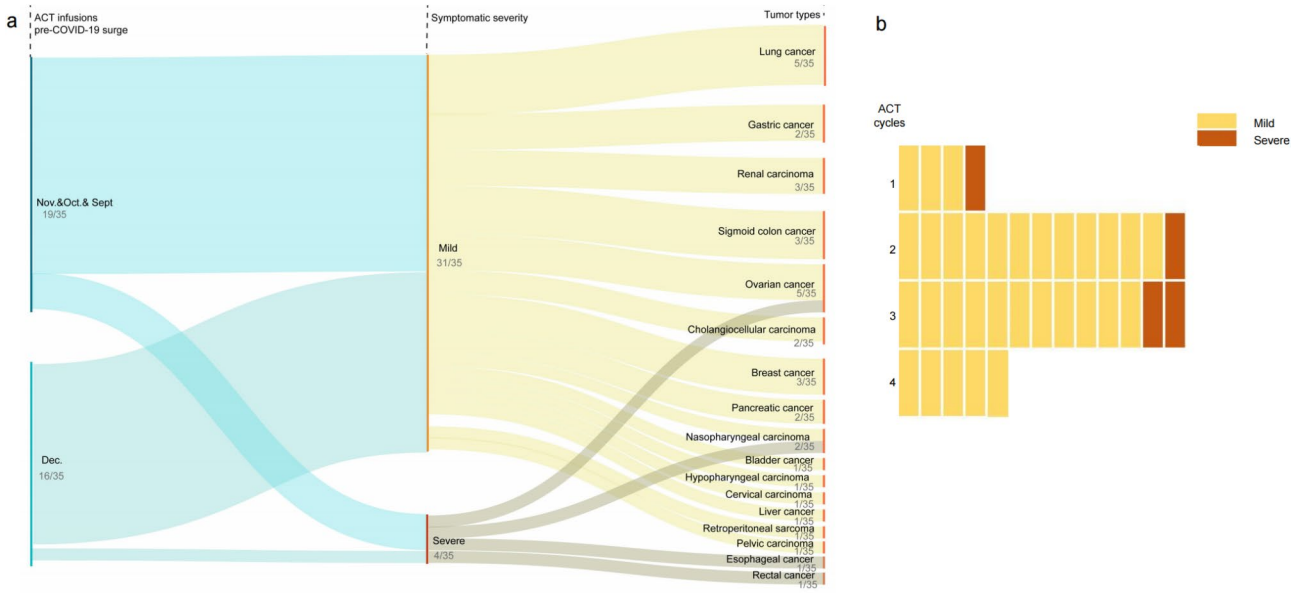

Fig. 2 Overall prevalence of ACT patients' distributions and severity of COVID-19 infections. **(a)** Prevalence of ACT infusions prior COVID-19 surge with subsequent symptom outcomes by Sanky analysis. The cases outbreak occurred during the December 2022 trends to COVID-19 surge in Shanghai and Beijing, we have compared the roles of last ACT infusion prior to the end of December, 3 cases (35 – 16 = 19, 3/19,15.8%) in October and November developed the severe symptomatic manifestations whereas there was 1 case in December (1/16, 6.3%). **(b)** Correlation of ACT infused cycles with clinical symptomatic distributions. Characteristics of ACT patients cohort, including ACT cycles and symptom severity ($n = 35$)

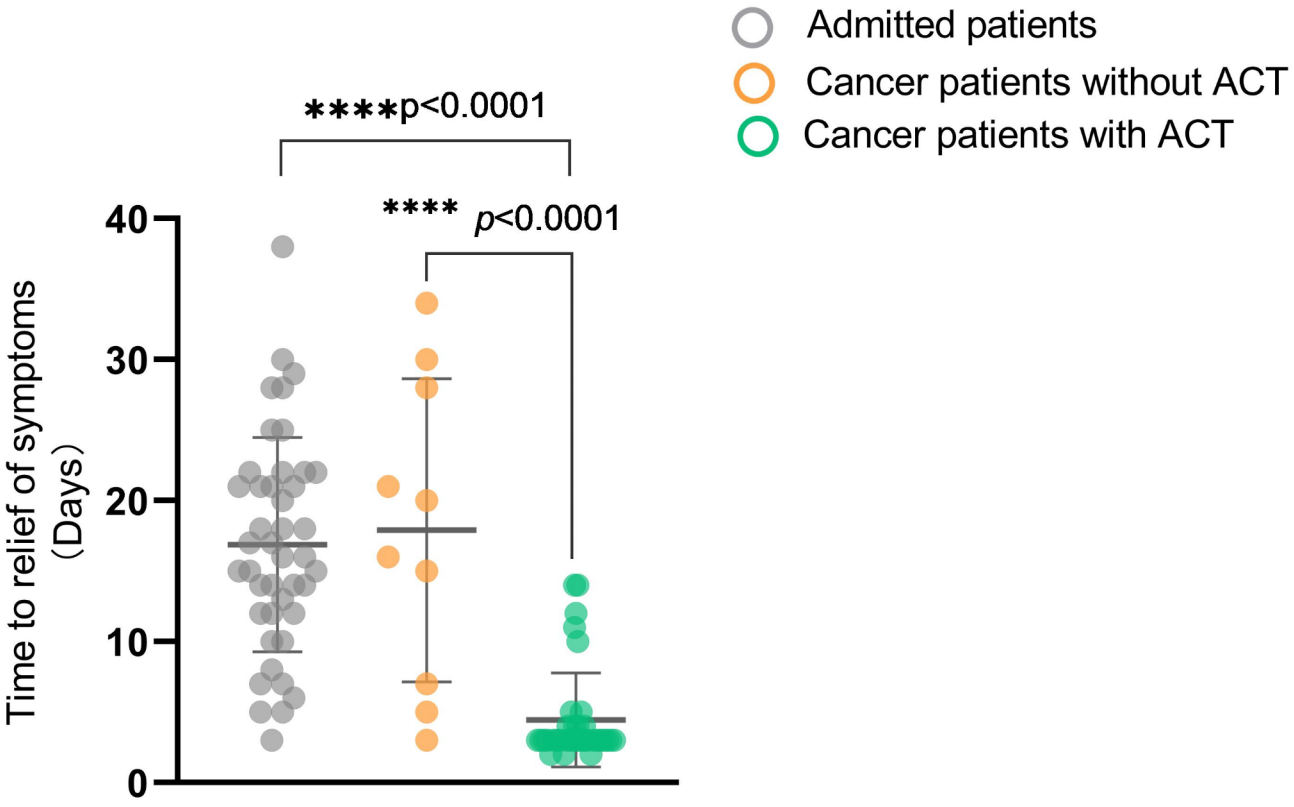

Fig. 3 Comparison of time to relief of symptoms by patients infected with COVID-19. The ACT was able to improve mean time to symptomatic alleviation from 17.9 days and 16.88 days to 4.46 days regardless of cancer or non-cancer patients (admitted patients, $n = 43$; cancer patients without ACT, $n = 10$; admitted patients, $n = 35$). All data are mean ± SEM. Statistical significance was tested with one- way ANOVA

Peripheral blood lymphocytes frequencies before and after ACT infusion

We analyzed the lymphocyte subsets of 6 selected patients in the ACT cancer patients to observe the variations of the peripheral blood immune phenotype before and after COVID-19 (Fig. 4). The results showed that there were no significant changes in B cells (Fig. 4a), T cells (Fig. 4c), CD4 + T cells (Fig. 4d), CD8 + T cells (Fig. 4e), and CD4+/CD8 + ratio (Fig. 4f) of post ACT, while NK cell was significantly increased ($p = 0.0017$, Figure 4b).

Influences of CIK-T cellamount and time to symptom alleviation

A retrospective study was conducted to compare the relationship between the total number of ACT cells infused and the time to alleviation of symptoms in the ACT group. The results showed that the greater the number of transfused T cells, the shorter the duration of symptoms ($P = 0.2869$, $R^2 = 0.05379$, Fig. 5).

Effect of ACT on the severe to mild shift and blood cell count

We have collected and analyzed the clinical cases who underwent the disease symptom alteration when exposed to ACT therapeutics.The data was represented by the occurrence possibility correlated with CIK-T cell infused amount.Although there was not difference of apheresis and CIK-T cell preparation regardless of types of cancer, the breakout of COVID-19 and inconvenience of CIK-T cellinfusion schedule risen from those inevitable interruption, leading to the frequency of ACT infusion variance during this three-month clinical observation study. The amount of infused CIK-T cell was associated with lowered risk of severity. Meantime there was no

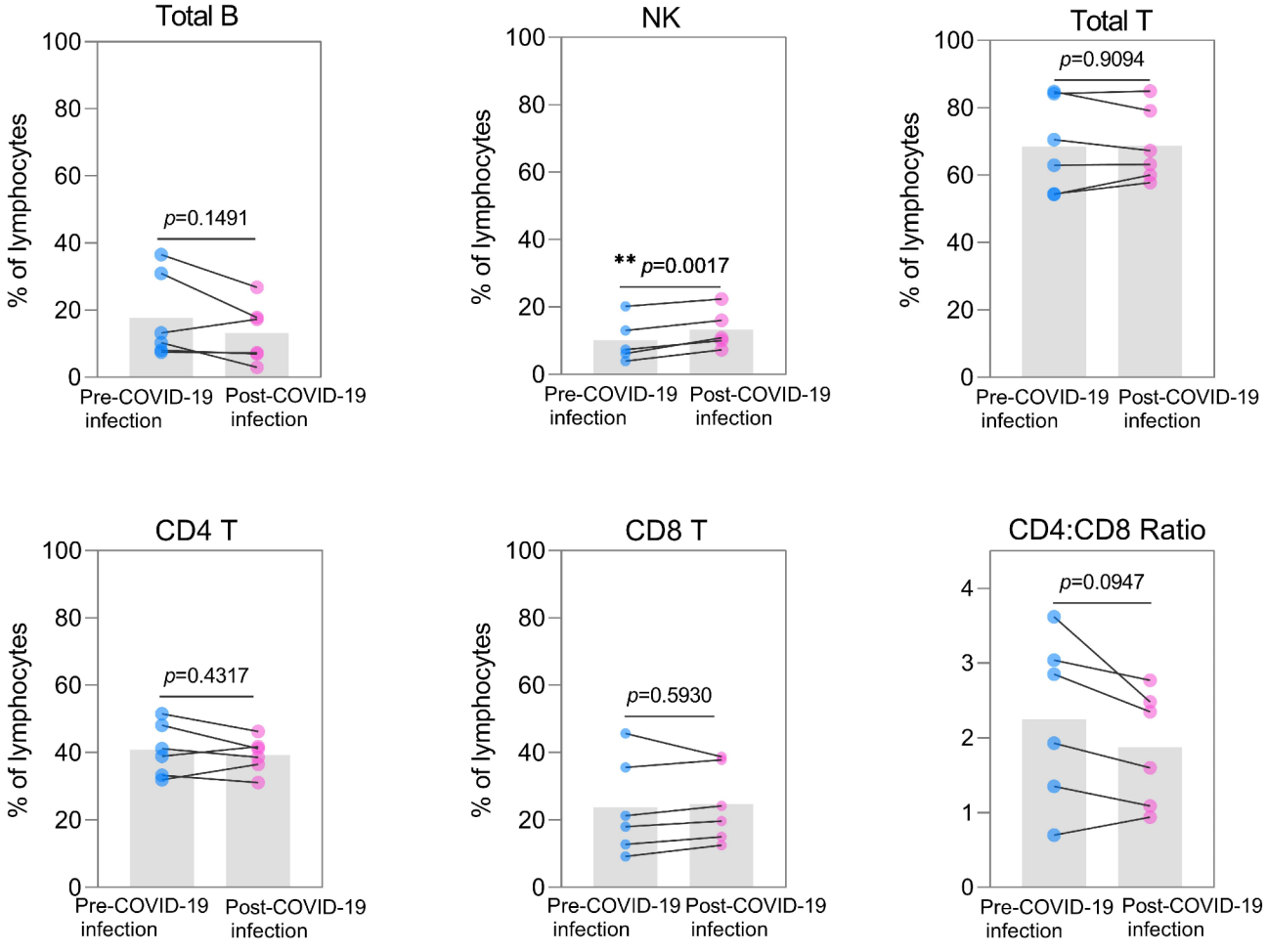

Fig. 4 Potential effects of ACT on peripheral blood immune phenotype on selected 6 cancer patients. **(a)** CD3-CD19 + lymphocytes subset of peripheral blood in patients ($n = 6$). **(b)** CD3-CD16 + CD56 + lymphocytes subset of peripheral blood in patients ($n = 5$). **(c)** CD3 + lymphocytes subset of peripheral blood in patients ($n = 6$). **(d)** CD4 + lymphocytes subset of peripheral blood in patients ($n = 6$). **(e)** CD8 + lymphocytes subset of peripheral blood in patients ($n = 6$). **(f)** CD4:CD8 ratio of peripheral blood in patients ($n = 6$). All data represent the means ± SEM. Statistical significance was tested with two-tailed paired Student's t test

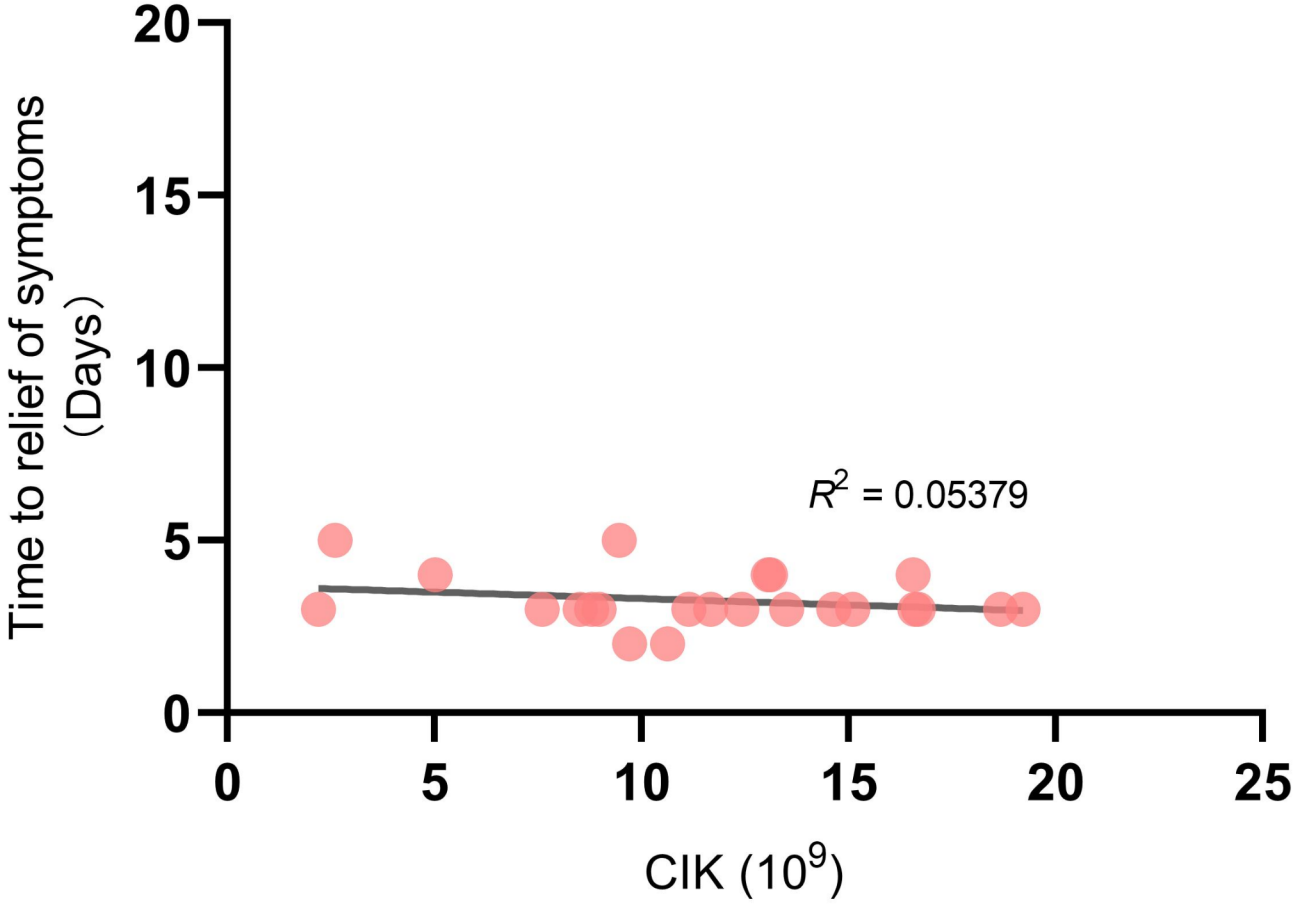

Fig. 5 Influences of number and time of ACT infusion on time to relief of symptoms. Correlation of total number of CIK infused with time to relief of symptoms, the mean time of ACT treated cancer patients was 4.46 days which were shorter than cancer patients without ACT ($p = 0.2869$)

difference of blood cell count while CIK-T cell infusions (Table 2).

Discussion

Immunity has the crucial roles in the conditions of injection and cancer. For instance those patients with inborn immune deficiency has hereditary antibody impairment, the vaccination of COVID-19 could elicit the hormonal immune response and antibody production [20]. Reina-Campos has reviewed the breakthrough findings of T cells metabolism, indicating that cancer or chronic viral infection drives CD8 + T cells into dysfunctional states, the anti-tumour CD8 + T cell response is further repressed by an immunosuppressive environment, preventing control of tumour growth [21].In one cohort study of 2515 adult patients with cancer and COVID-19, hematological malignant neoplasms and lung cancer were associated with increased mortality. No association was found between recent treatment with chemotherapy and overall or COVID-19–specific mortality, and treatment with immunotherapy before COVID-19 diagnosis was associated with a significant reduction in mortality [22]. In the view of attention of COVID-19 on population infection and mortality, there were declined to address the complication and various diseases linked clinical outcome.In actuality we have addressed that there were still emerging long-term investigations of COVID-19 on those chronic diseases. Immunodeficiency was risen from cancer progression and T cell exhaustion which subsequently affect the clinical outcome of anti-cancer treatment. Cancer patients have been observed to have a greater risk of more severe COVID-19, We have demonstrated that ACT added to chemotherapy improves the outcome for patients with a variety of solid tumors. Interestingly for lung cancer patients, the less severity cases were seen followed by the ACT treatment in the present group. No death cases in the cancer with ACT group. Possible explanations include reconstituting immunity damaged by chemotherapy as well as direct anticancer effects of the adoptive transferred cells. The past year COVID-19 surge in China provided an opportunity for us to study the safety profiles of ACT on the infected cancer patients as well as the severity of COVID-19 in cancer

patients because we continued our ACT program despite the surge.

We observed that there were not safety threatened occurrence during the scheduled ACT immunotherapy even during the COVID-19 infection status.Interestingly we have noticed that the severity and mortality rate of cancer patients who received ACT infusions was significantly lower than those of cancer patients and non-cancer patients without ACT. In fact, although the tumor patients who received ACT infusion were slightly younger, only 4 patients who received ACT infusion developed into severe cases, and no death cases occurred, compared with the previously reported cases of infection in the same age group (including COVID-19 pneumonia without underlying disease), there was a significant improvement (Table 1; Fig. 2). Some studies have shown that in patients with COVID-19, T lymphocyte depletion is the cause of severe disease and death [23]. Our research shows that ACT infusion significantly reduces the duration of symptoms of COVID-19 pneumonia (Fig. 3). The concurrent anti-cancer treatment with ACT could dramatically improve the time to symptom alleviation from 17.9 to 4.46 days. We further investigated the effects of ACT exposure on peripheral blood immune cell phenotype in 6 selected cancer patients we found that there was no significant change in T lymphocyte subsets before and after ACT except for apparent NK cells elevated which might be important for reducing severe cases and shortening the duration of symptoms persistence.We also summarized the peripheral blood cell count, there was not impact of ACT on blood cell count.Given the considerations of COVID-19 vaccination on the symptom substantial effects, we have compared that 4 cases of ACT-cancer group were vaccinated, and there were not different among those groups, it could be explained that the ACT had played the key immunological roles in the infectious setting. We have concentrated on the clinical symptomatic associated effect of ACT, while repetitive CIK-T cellinfusions could improve the T cell exhausting and might restore the immunosuppression status caused by both active COVID-19 infection and chronic cancer suffering. While the concurrent planned ACT combination with chemotherapy, patients were continuously received the standard chemotherapy as pre-COVID-19 infection. There were not seriously hematological adverse responses cases who were directly linked with the chemotherapy. Few cancer patients were encountered neutropenia and thrombocytopenia as commonly seen in the chemotherapy. As this clinical observation study, we have addressed the event concurrence within the 3 month interval during the COVID-19 mounting, the scheduled ACT infusion could result in the increased possibility for severe to mild shift trend.

There are some commitments that all physicians have a responsibility to provide the best care to their patients. These data suggest that cancer patients who are at high risk for COVID-19 infections may benefit from a discussion about banking activated T cell products should they become infected with COVID-19. The limitations of this study include only collecting a limited number of cases of COVID-19 pneumonia infection since November 2022. As for the non-ACT oriented admitted patients, the hospitalized criteria was mainly arisen from the severe symptoms, who were more popularized than cancer with pre-ACT. Cancer patients enrolled were not randomized to be distinguished from cancer with ACT and cancer without ACT. Despite these limitations, our study reevaluates the importance of ACT infusion in reducing the severity and mortality of COVID-19.

Limitations This study has conducted the retrospective cases summary, although we have primarily explored to find the clinical impact and potential benefit of ACT on cancer patients, all three groups were not randomly enrolled which definitely rise some study bias. We were encouraged to demonstrate the death situation of cancer with ACT rather than for concentration on comparison between three groups. Although we have standard quality control and operation of apheresis and CIK-T cell inductions in vitro, the non equilibrium original apheresis storage could cause the difference of CIK-T cell infused within the 3 months of pandemic breakout.The average age above 65 years old has accounted for main percentage among the regular admitted population which had higher mortality. Therefore, we have focused on the data analysis on cancer with ACT to provide the clinical symptomatic data in COVID-19 infection situation, hopefully those data could provide the prophylactic strategy when caner patients with infectious disease complications.

Conclusions

These data suggest both the safety and potential therapeutic roles of ACT for cancer patients with COVID-19 infection status.The additional ACT during the infectious status could simultaneously leverage and reduce the risk of disease severity.

Abbreviations

ACT	Adoptive cellular immune-therapeutic
aCCI	Age-adjusted Charlson comorbidity index
DC	Dendritic cell
CIK-T cell	Cytokine induced killer T cell
TCR	T cell receptor
COPD	Chronic obstructive pulmonary disease
HIN	Hypertension
CHF	Congestive heart failure
DM	Diabetes mellitus
CKD	Chronic kidney disease
HC	Liver cirrhosis
CI	Cerebral infarction

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Author contributions
Congcong Li: Writing-review & editing, Writing-original draft, Investigation, Formal analysis, Data collection, Conceptualization. Dazhao Xu: Writing-review & editing, Writing- original draft, Methodology, Investigation, Formal analysis, Data collection, Conceptualization. Linyao Lu: Software Formal analysis. Shu Peng: Data analysis and draft support of reference.Haiyang Zhao: Writing review & editing, Writing original draft, Methodology, Investigation, Formal analysis, Data curation.Chuxiong Zeng: Clinical data collection, patients care.Lina Hu: Clinical data collection, patients care. Xianzhi Guo: Clinical data collection, patients care. Li Liu: Clinical data collection, patients care.Feifei Huo: Clinical data collection, patients care. Xiumei Rong: Clinical data collection, patients care.Zhenying Geng: Clinical data collection, patients care. Ping Lin: Clinical data collection, patients care. Xinna Zhou: Project administration, Investigation, Formal analysis.Xiaoli Wang: Clinical data collection, patients care. Amy Hobeika: Project administration, Investigation, Formal analysis. Michael A Morse: Project administration, Investigation, Formal analysis, draft modificatiton, data correction.Herbert Kim Lyerly: Conceptualization, project administration, investigation, formal analysis, draft modification.Jun Ren: Supervision, Investigation, Funding acquisition, Conceptualization. Writing–review & editing.

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

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of Fudan University Pudong Medical Center, Shanghai, China. Ethics number: 2021-IIT-021-E02.

Consent for publication
Written informed consent to participate in this study was obtained from all patients at the time of admission.

Competing interests
The authors declare no competing interests.

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