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Tofacitinib for the treatment of immune-related adverse events in cancer immunotherapy: a multi-center observational study

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Abstract

Background Treatment strategy against immune-related adverse events (irAEs) induced by immune checkpoint inhibitors (ICIs) frequently requires other immunosuppressive agents. Tofacitinib is a rapidly acting JAK-STAT inhibitor with proven efficacy in multiple autoimmune diseases. We aimed to evaluate the efficacy and safety of tofacitinib in the management of irAEs in cancer patients.

Methods Cancer patients who received ICIs and were treated with tofacitinib for the management of irAEs at 6 institutions were retrospectively included in this study. Demographic and clinical characteristics were obtained from electronic medical records. Longitudinal assessment of cardiac troponin T (cTnT) with clinical assessment was utilized to evaluate the benefit of tofacitinib treatment in patients with ICI myocarditis. Overall survival (OS) was also assessed.

Results Fifty-three patients were included in this study. The median time from irAE onset to tofacitinib therapy was 17 (range, 2–186) days and the median duration of tofacitinib treatment was 52.5 (range, 3–277) days. Enrolled patients were subdivided into 3 groups based on clinical severity and steroid responsiveness including 11 life-threatening cases, 30 steroid-resistant cases, and 12 cases with steroid taper failure. Clinical remission rate in each group was 54.5%, 96.7%, and 100%, respectively ($P < 0.01$). Tofacitinib was well-tolerated with 4 patients (7.5%) developing infectious events. From the ICI initiation, the overall median OS was 16.1 (95% CI 7.8–26.9) months.

Conclusion Tofacitinib showed promising clinical efficacy in patients experiencing irAEs, particularly in patients who failed to respond to steroids or experienced relapse during steroid tapering. Moreover, and most importantly, tofacitinib exhibited a favorable safety profile in cancer patients developing irAEs in terms of both toxicity and anti-tumor activity. Future prospective studies are warranted.

Keywords Immune-related adverse events, Immunotherapy, Myocarditis, Tofacitinib

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Introduction

Immune checkpoint inhibitors (ICIs), which target cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD-L1), have changed the landscape of cancer treatment in the past decade [1]. Recently, interest has grown in other immune checkpoints and novel potential targets such as TIM-3, LAG-3, and TIGIT are also under investigation [2]. However, the increasing use of ICIs is accompanied by a broad spectrum of immune-mediated toxicities, termed immune-related adverse events (irAEs) [3]. Among these, cardiotoxicity such as myocarditis is a rare but potentially fatal side effect [4]. Although the precise pathophysiology has not been fully elucidated, proposed mechanisms underlying irAEs might involve the breach of immune tolerance, cross-antigen reactivity, proinflammatory cytokines, and the microbiome [5].

Currently, each cancer society has published its own guidelines in terms of the treatment of irAEs, which all recommends corticosteroids as the first-line therapy, with distinct immunosuppressive therapy applied for cases that are refractory to corticosteroids [6, 7]. Strategies include tumor necrosis factor (TNF)-α inhibitor infliximab, the interleukin (IL)-6 receptor inhibitor tocilizumab, and the CTLA-4 agonist abatacept, which have been reported to induce remission in refractory or severe irAE cases. Current guidelines (ASCO, ESMO, SITC, NCCN) also recommend other immunosuppressive agents for immune-related myocarditis (irMyocarditis), such as mycophenolate mofetil, ruxolitinib, anti-thymocyte globulin (ATG), and alemtuzumab [6–10]. However, this strengthened immunosuppressive strategy has raised concerns about an increased risk of serious infection and a potential reduction in the antitumor efficacy of ICIs in cancer patients [11].

The Janus kinase–signal transducer and activator of transcription (JAK–STAT) signaling pathway is an important regulator of both innate and adaptive immunity and has potential implications in autoimmunity and cancer immune surveillance [12]. Tofacitinib is an oral, rapidly acting, small-molecule JAK inhibitor that preferentially inhibits JAK 1 or JAK3 [13]. Increasing evidence has shown its clinical efficacy in multiple autoimmune diseases and inflammatory disorders, including rheumatoid arthritis and inflammatory bowel disease [14, 15]. Notably, tofacitinib has also been approved for the management of COVID-19, without any higher risks of secondary infection or thromboembolic events [16]. The treatment effects of tofacitinib in refractory irAEs have been reported in case series, particularly in ICI-related colitis [17, 18]. However, the clinical use of tofacitinib in the context of irAEs and long-term cancer outcome is still largely unexplored.

In this study, we report on our multicenter experience utilizing tofacitinib in the treatment of irAEs across various cancer types. Additionally, we aim to provide some insights into the management of irAEs guided by the stratification of clinical severity and steroid sensitivity.

Methods

Study population and definition of irAEs

Cancer patients who received ICIs and were treated with tofacitinib for any grade irAEs from August 2019 to March 2023 at 6 institutions were retrospectively included in this study. IrAEs were defined by the treating medical oncologist and confirmed by the multidisciplinary team after alternative diagnoses were excluded, based on either pathologic, radiographic, and clinical evidence of irAEs or clinical improvement with irAE-based treatment. This study complies with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Zhongshan Hospital affiliated to Fudan University and each institution (Approval No. B2023-178).

Data collection

Demographic and clinical data from enrolled patients were extracted from electronic medical records, including social information, oncologic history, laboratory tests, ICI treatment, irAEs, and relative treatment, adverse effects, and clinical outcomes (details are shown in the supplementary table).

The primary study endpoint was clinical improvement of irAE in cancer patients treated with tofacitinib (defined as irAE resolution to grade 1 according to Common Terminology Criteria for Adverse Events [CTCAE] v5.0). The secondary endpoints of this study included safety of tofacitinib and cancer outcome [overall survival (OS)]. OS was calculated from the time of ICI initiation until death, with censoring on the last known date alive. The beginning of follow-up was the time of diagnosis of irAEs and the end of follow-up date was on 21st March 2024. Longitudinal assessment of cardiac troponin T (cTnT) and clinical assessment were utilized to measure the primary endpoint in irMyocarditis patients.

The patients were categorized into 3 groups based on the clinical scenarios of tofacitinib use in the management of irAEs, including: (1) life-threatening consequences (grades 4–5 according to CTCAE v5.0), (2) steroid resistance, which was defined as only partially remission or no response after the patient received the highest recommended dose of corticosteroid therapy as per the guidelines [7, 19], and (3) steroid taper failure, which was defined as a relapse of symptoms or laboratory test results during steroids tapering. For patients with irMyocarditis, life-threatening consequence is

characterized by hemodynamic or electrical instability as fulminant cases [19]. In addition, steroid resistance was confirmed if there were no significant reductions in troponin level (50% reduction from peak) and/or AV block and ventricular arrhythmias persist despite 3 days of i.v. methylprednisolone, in accordance with the 2022 ESC Guidelines on cardio-oncology [19].

Statistical analysis

Continuous variables were described as mean ± standard deviation or as median (range), depending on their distribution. Student's *t*-tests or Mann–Whitney *U*-test were used for comparison based on data normality. Categorical variables are expressed as percentages and compared using the chi-square or Fisher's exact test. Kaplan–Meier curves for OS by clinical outcome and treatment groups were presented and compared with Cox proportional hazard regression model. Statistical significance was defined as a two-sided p-value < 0.05. All analyses were performed using R (version 4.2.0) [20].

Results

Patient characteristics and spectrum of irAEs

The study enrolled a total of 53 patients between August 2019 and March 2023, 46 of whom were from the Department of Oncology, Zhongshan Hospital, while the remaining 7 patients were from 5 other institutions. Clinical characteristics of the patients are presented in Table 1. The mean age at the initiation of ICIs therapy was 64.9 ± 10.0 years, and 33 (62.3%) of the patients were male. Hypertension was the most prevalent comorbidity among the patients, and none had a history of autoimmune diseases. The most common indications for ICI treatment in our cohort were gastric, lung, and liver cancer, accounting for 31 patients (58.5%). The majority of patients (94.3%) received single ICI therapy, either PD-1 or PD-L1 inhibitor. Dual ICI therapy was administered in 3 patients. Among these patients, 10 (18.9%) were treated with ICIs alone, while 43 (81.1%) received a combination of ICIs with chemotherapy, targeted therapy, or both. The median time from the initiation of ICI therapy to irAEs onset was 34 (range, 11–861) days, and the median number of ICI doses received was 2 (range, 1–31).

Tofacitinib was administered in 53 patients for the management of irAEs induced by ICI treatment. The toxicity profile of irAEs is presented in Fig. 1. The most common irAEs identified in this cohort were myocarditis (n = 48, 91%), myositis (n = 30, 57%), and hepatitis (n = 22, 42%). Notably, for patients treated with tofacitinib, irAEs usually involved two or more organs (n = 38, 72%). The most frequent concurrent multiorgan irAE patterns for tofacitinib treatment in our cohort were myocarditis myositis hepatitis (n = 18, 34%), followed by myocarditis myositis (n = 12, 23%). Additionally, six patients with ICI-associated myocarditis and myositis also presented with myasthenia gravis-like symptoms.

Table 1 Clinical characteristics of 53 irAE patients treated with tofacitinib

	All cases (N = 53)
Age (mean [SD])	64.9 (10.0)
Male, No. (%)	33 (62.3)
Comorbidity, No. (%)	
HBP	25 (47.2)
DM	12 (22.6)
CAD	6 (11.3)
AD	0 (0.0)
Cancer type, No. (%)	
Biliary	2 (3.8)
Colorectal	4 (7.5)
Esophageal	2 (3.8)
Gallbladder	3 (5.7)
Gastric	14 (26.4)
Hepatic	7 (13.2)
Nasopharyngeal	1 (1.9)
Pulmonary	10 (18.9)
Renal	1 (1.9)
Others	9 (17.0)
ICI type, No. (%)	
Anti-PD-1	46 (86.8)
Anti-PD-L1	4 (7.5)
Anti-PD-L1 + anti-CTLA-4	2 (3.8)
Anti-PD-L1 + anti-TIGIT	1 (1.9)
Tumor stage, No. (%)	
Stage III	5 (9.4)
Stage IV	48 (90.6)
Treatment regimen, No. (%)	
ICI	10 (18.9)
ICI + CT	22 (41.5)
ICI + TT	13 (24.5)
ICI + CT + TT	8 (15.1)
Time to irAE onset (days) (median [range])	34.0 (11–861)
Doses of ICI (median [range])	2.0 (1–31)

irAE immune-related adverse event, *SD* standard deviation, *HBP* hypertension, *DM* diabetes mellitus, *CAD* coronary atherosclerotic heart disease, *AD* autoimmune diseases, *ICI* immune checkpoint inhibitor, *PD-1* programmed cell death 1, *PD-L1* programmed death-1/ligand-1, *CTLA-4* cytotoxic T lymphocyte antigen-4, *TIGIT* T cell immunoreceptor with Ig and ITIM domains, *CT* chemotherapy, *TT* targeted therapy

Tofacitinib treatment for the management of irAEs based on clinical severity and steroid sensitivity

The patients were stratified into three groups based on the clinical severity and steroid sensitivity, including 11 cases defined as life-threatening consequences, 30

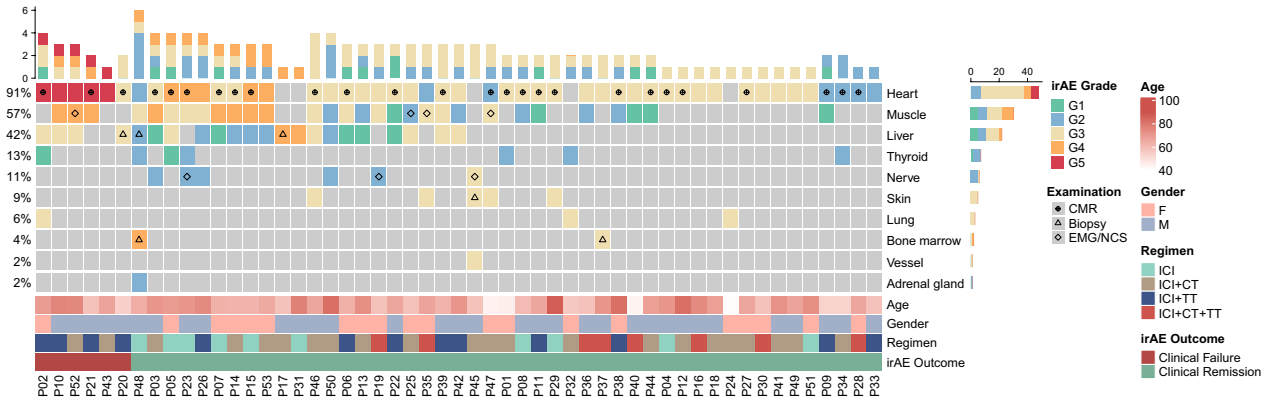

Fig. 1 Heatmap displaying irAE profiles of 53 patients with tofacitinib treatment. Patients were grouped by the clinical outcome of irAE and ranked by the severity of irAE and the number of organs involved. Each cell marked with symbols indicates the irAE was confirmed by the corresponding examination. *IrAE* immune-related adverse event, *CMR* cardiovascular magnetic resonance, *EMG/NCS* electromyography, and nerve conduction study, *F* female, *M* male, *ICI* immune checkpoint inhibitor, *CT* chemotherapy, *TT* target therapy

cases that were steroid-resistant, and 12 cases who had relapsed symptoms or laboratory test results during steroid tapering (Table 2). The clinical course for irAE treatment of each patient is presented in Fig. 2.

IrAEs were initially treated with corticosteroids in all patients either orally or intravenously, according to published guidelines, with tofacitinib administered at different dosages (5 mg, QD-BID-TID, Table 2). The dose of corticosteroid was converted to methylprednisolone equivalents. The median time from irAE onset to steroid initiation was 5 (range, 0–81) days, 2 (range, 0–81) days, and 15 (range, 0–53) days in the three groups, respectively ($P=0.33$). Almost all patients with life-threatening consequences were treated with a higher initial dose of corticosteroids (at least 100 mg methylprednisolone per day), and 81.8% of the patients were treated with 500 or 1000 mg methylprednisolone per day as initiation. Most patients with steroid resistance or steroid taper failure received less than 4 mg/kg methylprednisolone per day as initiation, the maximum dosage threshold used in steroid-resistant group was 500 mg methylprednisolone per day. The median duration of steroid treatment was 59 (range, 6–92) days for patients with life-threatening consequences, 67 (range, 16–284) days for patients with steroid resistance, and 114 (range, 52–233) days for patients with steroid taper failure ($P<0.01$). As for tofacitinib initiation, the median time was 8 (range, 2–84) days, 13 (range, 6–144) days, and 35 (range, 20–186) days after irAE onset in the three groups, respectively ($P<0.01$). The dosage of tofacitinib was mainly 5 mg twice a day in all three groups. One-fourth of the patients received 5 mg of tofacitinib once a day, and only one patient with fulminant irMyocarditis received tofacitinib 5 mg three times per day. The median duration of tofacitinib administration was 31 (range, 3–92) days for patients with life-threatening consequences, 49 (range, 7–277) days for patients with steroid resistance, and 78.5 (range, 14–186) days for patients with steroid taper failure, respectively ($P=0.08$).

In addition to tofacitinib, other immunosuppressive therapies were also utilized in our cohort. Intravenous immune globulin (IVIG) was administered to 72.7% of patients in the life-threatening consequence group, 56.7% in the steroid resistance group, and 41.7% in the steroid taper failure group. Tocilizumab was applied in 2 patients with fulminant myocarditis; one achieved clinical remission and the other died of irAE. Of note, the patient who survived from fulminant myocarditis (malignant ventricular arrhythmia) exhibited rapid clinical improvement only after receiving abatacept treatment, neither tofacitinib nor tocilizumab therapy had a positive effect on the patient's condition. Twenty-one (39.6%) patients in this cohort were treated with tofacitinib as the first immunosuppressive agent, while 32 (60.4%) received more than one form of immunosuppressive therapy. Among these, the majority used tofacitinib as a second-line immunosuppressive agent following IVIG therapy.

In terms of clinical outcome for irAEs, 54.5% of patients in the life-threatening consequence group, 96.7% in the steroid resistance group, and 100% in the steroid taper failure group achieved clinical remission ($P<0.01$). Less than 8% of patients (n = 1, 2, and 1 in the three groups, respectively) developed confirmed infectious adverse events during combined immunosuppressive therapy.

Tofacitinib treatment in irMyocarditis

Troponin T levels were available in 42 out of 48 irMyocarditis patients. Higher level of cTnT before steroid

Table 2 Treatment for irAE of 53 patients stratified by the clinical severity and steroid sensitivity

	All cases (N = 53)	Life-threatening consequence (N = 11)	Steroid resistance (N = 30)	Steroid taper failure (N = 12)	*P*
Numbers of irAE involved organs, No. (%)					
1	15 (28.3)	2 (18.2)	11 (36.7)	2 (16.7)	0.21
2	14 (26.4)	1 (9.1)	8 (26.7)	5 (41.7)	
≥ 3	24 (45.3)	8 (72.7)	11 (36.7)	5 (41.7)	
irAE grade, No. (%)					
G2	4 (7.5)	0 (0.0)	3 (10.0)	1 (8.3)	< 0.01
G3–4	44 (83.1)	6 (54.5)	27 (90.0)	11 (91.7)	
G5	5 (9.4)	5(45.5)	0 (0.0)	0 (0.0)	
Time to steroid initiation (days) (median [range])	4 (0–81)	5 (0–81)	2 (0–81)	15 (0–53)	0.33
Initial dose of steroid, No. (%)					
10–20 mg/day	5 (9.4)	0 (0.0)	5 (16.7)	0 (0.0)	< 0.01
0.5–1 mg/kg/day	9 (17.0)	0 (0.0)	5 (16.7)	4 (33.3)	
1–2 mg/kg/day	13 (24.5)	2 (18.2)	7 (23.3)	4 (33.3)	
2–4 mg/kg/day	11(20.8)	0 (0.0)	8 (26.6)	3 (25.0)	
500–1000 mg/day	15 (28.3)	9 (81.8)	5 (16.7)	1 (8.4)	
Duration of steroids (days) (median [range])	71 (6–284)	59 (6–92)	67 (16–284)	114 (52–233)	< 0.01
Time to tofacitinib initiation (days) (median [range])	17 (2–186)	8 (2–84)	13 (6–144)	35 (20–186)	< 0.01
Dosage of tofacitinib, No. (%)					
5 mg qd	13 (24.5)	1 (9.1)	9 (30.0)	3 (25.0)	0.30
5 mg bid	39 (73.6)	9 (81.8)	21 (70.0)	9 (75.0)	
5 mg tid	1 (1.9)	1 (9.1)	0 (0.0)	0 (0.0)	
Duration of tofacitinib (days) (median [range])	52.5 (3–277)	31 (3–92)	49 (7–277)	78.5 (14–186)	0.08
Other immunosuppressive therapy, No. (%)					
IVIG	30 (56.6)	8 (72.7)	17 (56.7)	5 (41.7)	0.36
Tocilizumab	2 (3.8)	2 (18.2)	0 (0.0)	0 (0.0)	0.04
Abatacept	1 (1.9)	1 (9.1)	0 (0.0)	0 (0.0)	0.21
Plasmapheresis	2 (3.8)	2 (18.2)	0 (0.0)	0 (0.0)	0.04
Cyclosporine A	2 (3.8)	0 (0.0)	2 (6.7)	0 (0.0)	1
Hydroxychloroquine	2 (3.8)	0 (0.0)	2 (6.7)	0 (0.0)	1
Tacrolimus	1 (1.9)	0 (0.0)	1 (3.3)	0 (0.0)	1
Mycophenolate mofetil	1 (1.9)	0 (0.0)	0 (0.0)	1 (8.3)	0.43
Number of immunosuppressive agents used, No. (%)					
1 (only tofacitinib)	21 (39.6)	3 (27.3)	13 (43.3)	5 (41.7)	0.69
≥ 2	32 (60.4)	8 (72.7)	17 (56.7)	7 (58.3)	
Line of tofacitinib, No. (%)					
1	21 (39.6)	3 (27.3)	13 (43.3)	5 (41.7)	0.89
2	28 (52.8)	7 (63.6)	15 (50.0)	6 (50.0)	
3	4 (7.5)	1 (9.1)	2 (6.7)	1 (8.3)	
irAE outcome, No. (%)					
Clinical failure	6 (11.3)	5 (45.5)	1 (3.3)	0 (0.0)	< 0.01
Clinical remission	47 (88.7)	6 (54.5)	29 (96.7)	12 (100.0)	
Infectious adverse events, No. (%)	4 (7.5)	1 (9.1)	2 (6.7)	1 (8.3)	1

Time to irAE onset refers the time from immune checkpoint inhibitor initiation to irAE onset. Time to steroid or tofacitinib initiation refers the time from irAE onset to steroid or tofatinib initiation. irAE grade refers the grade of the most severe one for patients with irAEs involved more than one organ

irAE immune-related adverse event, *IVIG* intravenous immune globulin

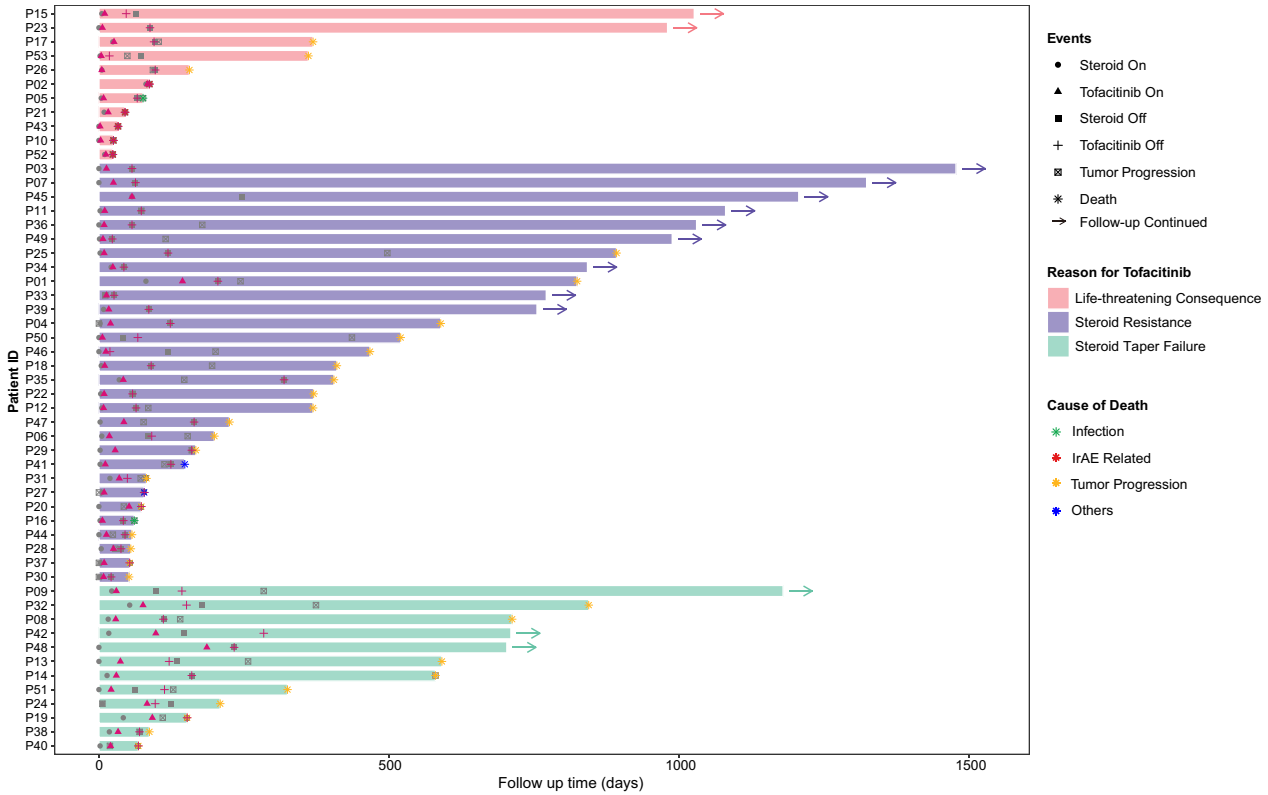

Fig. 2 Swimmer plot showing the timeline of irAE treatment events, tumor progression, and deaths from the onset of irAE stratified by the scenarios of tofacitinib use. Events (steroids on, tofacitinib on, steroid off, tofacitinib off, tumor progression, and death) are identified by differently shaped symbols on the columns. The colors of the death symbol indicate the causes of death. IrAE, immune-related adverse event

administration (baseline) was observed in the life-threatening consequence group compared to the steroid resistance and the steroid taper failure group (0.984 vs. 0.281 vs. 0.531 ng/ml, $P < 0.01$). The dynamic change of cTnT levels were plotted over time points including baseline, 3 days after steroid administration, the time before tofacitinib administration, 3 days after tofacitinib administration, 7 days after tofacitinib administration, and the time when tofacitinib was discontinued or the time of last available follow-up (Fig. 3). Relative levels of cTnT at each time point compared to the baseline per case were presented since the absolute value of cTnT level varied widely among patients.

For cases in the life-threatening group, cTnT levels slightly declined after initiation of tofacitinib treatment in 4/10 clinically improved patients. However, in 5 patients with fulminant myocarditis who failed to respond to neither steroid nor tofacitinib treatment, continuous decrease of cTnT level was not observed, indicating that dynamic surveillance of cTnT levels might be a predictor of cardiovascular mortality of irMyocarditis patients.

Ten out of 24 patients in the steroid resistance group showed higher levels of cTnT compared to the baseline after 3 days of initial steroid treatment, and the other 14 patients also showed unsatisfied decline of cTnT level. A mild to moderate decrease was observed immediately after administration of tofacitinib in the measured cTnT values in all patients in this group, suggesting the efficacy of tofacitinib treatment as an additional immunosuppressive agent in steroid-resistant irMyocarditis.

Eight patients with available cTnT data were shown in the steroid taper failure group. Even though these patients responded well to the initial steroid treatment, rebound of cTnT level occurred during steroid tapering. Administration of tofacitinib successfully resulted in the continuous decrease of cTnT level upon the following steroid tapering (Fig. 3).

Study outcome and safety of tofacitinib

Clinical remission was achieved in 47/53 patients (88.7%). Five patients with fulminant myocarditis failed to respond to tofacitinib in combination with high-dose corticosteroids and cardiovascular deaths occurred (Fig. 1). One patient with steroid-resistant hepatitis also showed no improvement after tofacitinib administration but died of cancer progression (Table 2).

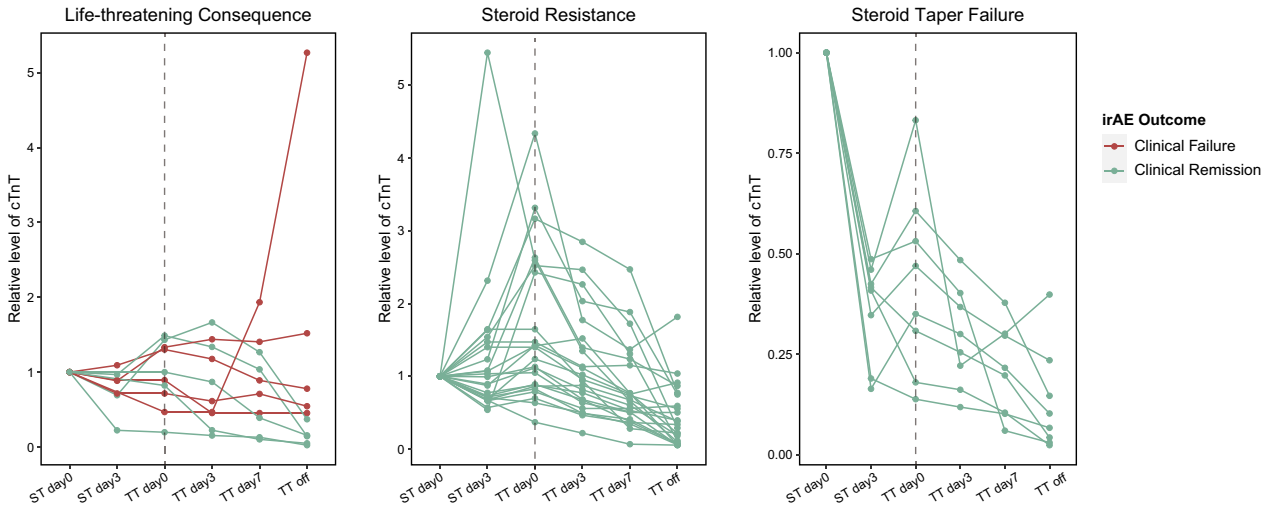

Fig. 3 Fold changes in the cTnT level from the initiation of steroid treatment to the end of tofacitinib treatment in patients with myocarditis grouped by the scenarios of tofacitinib use. cTnT levels at six key time points were presented. Patients in the steroid-resistance group and the steroid-taper-failure group exhibited a significant reduction in cTnT levels following tofacitinib treatment. *cTnT* cardiac troponin T, *ST* steroid treatment, *TT* tofacitinib treatment

Infection was reported in four cases with no thromboembolic events observed in the cohort. All four patients experienced pulmonary infection while two cases of death occurred due to septic shock. One of these patients developed severe pulmonary infection while on long-term tofacitinib treatment, after irAE had improved and steroid therapy had been discontinued. Additionally, one patient was diagnosed with pulmonary tuberculosis (confirmed by biopsy) one month after irAE had improved and both steroid and tofacitinib treatments had been discontinued. Although the patient initially responded to anti-tuberculosis treatment, he eventually died of tumor progression. Another patient developed pulmonary infection during irAE treatment. Despite intensified therapy with steroids and immunosuppressive agents, the irMyocarditis showed no improvement, and the patient ultimately died due to irAE.

ICI treatment was permanently discontinued in 52/53 patients (98.1%), and rechallenged in 1 steroid-resistant hepatitis patient due to the clinical response to ICI treatment. However, this patient developed recurrent ICI-related hepatitis after 3 doses of ICI administration.

During a median follow-up of 35.8 (95% CI, 35.0-NR) months from ICI initiation, 30 patients had deceased, 21 of whom died of tumor progression. Other reasons for cause of death include ICI-induced adverse events (n = 5) and infection (n = 2). Two patients died for unknown reasons (Fig. 2). The overall median OS was 16.1 (95% CI 7.8–26.9) months. Patients in the life-threatening group presented inferior OS compared to the steroid resistance and the steroid taper failure group (median months: 4.0 vs 16.6 vs 22.8; log-rank P = 0.07). Using the cox proportional hazard model adjusting for ICI duration, age, and sex, no significant differences in OS were observed between steroid resistance (hazard ratio [HR] 0.53, 95% CI [0.23, 1.20], P = 0.13) and steroid taper failure group (HR 0.53, 95% CI [0.20, 1.38], P = 0.19) compared to life-threatening group (Fig. 4).

Discussion

This study provides a comprehensive overview of our initial experience using tofacitinib as an additional immunosuppressive therapy for irAEs. In our cohort, tofacitinib demonstrated promising results, with clinical remission achieved in 54.5% of patients with life-threatening irAEs, 96.7% of patients with steroid resistance, and 100% of patients with steroid taper failure. Noteworthy, we did not observe any increased risk of infection or thromboembolic events with tofacitinib administration. Furthermore, the anti-tumor efficacy of ICIs seems not to be compromised by tofacitinib treatment. To the best of our knowledge, this is the largest clinical study to demonstrate that tofacitinib, a JAK-STAT inhibitor, can be safely used for the treatment of irAEs.

The incidence of irMyocarditis ranges from 0.1 to 1.1% with a case fatality rate up to 40% [21]. In our cohort, tofacitinib demonstrated promising results, with clinical remission achieved in 87.5% of irMyocarditis patients. This may also be attributed to the early detection and treatment of irMyocarditis. These findings underscore the need for further prospective and comparative studies to explore the efficacy of this therapeutic strategy.

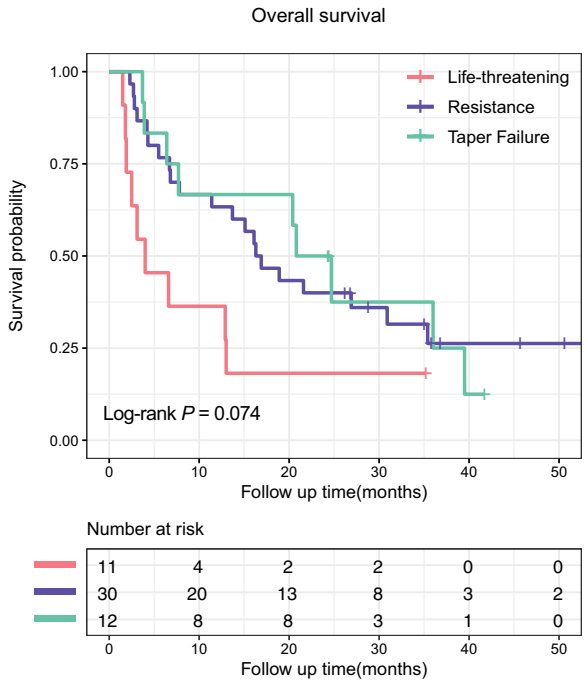

Fig. 4 Kaplan–Meier curves for overall survival (OS) in this cohort grouped by the scenarios of tofacitinib use. Patients with life-threatening irAE demonstrated poorer survival. A log-rank p-value was calculated comparing survival across the defined groups

The inhibition of the JAK–STAT signaling pathway has yielded remarkable remissions in primary autoimmune conditions [14, 15]. The strategies employed for managing irAEs share considerable parallels with those utilized in the context of primary autoimmune diseases. Tofacitinib is an oral inhibitor selectively targets the signaling pathways downstream of JAK1 and JAK3, which also modulates the action of interferon (IFN)-γ and IL-6, downregulating subsets of T helper (Th) 1 and Th17 cells [22, 23]. Currently, tofacitinib has been clinically used for the treatment of ulcerative colitis and rheumatological diseases such as rheumatoid arthritis and psoriatic arthritis [24, 25]. A recent study utilizing single-cell analysis has shed light on the underlying mechanism of ICI-colitis, identifying activated $CD8^+$ T_{RM} (tissue resident memory T) as the key effector which prominently express checkpoint proteins and IFN-γ. Given the up-regulated IFN-γ signaling, tofacitinib has been proposed as a potential therapeutic option for the treatment of ICI-colitis [26]. Bulk RNA-sequencing has also been used to compare transcriptomics profile in endomyocardial biopsies from patients with irMyocarditis with those from patients with virus-induced myocarditis and dilated cardiomyopathy, and IFN-γ pathway was found to be up-regulated in ICI-associated myocardial samples [27]. Another bulk RNA-seq study using irMyocarditis mouse models (ctla4 ± pd1−/−) and endomyocardial biopsy samples from patients with irMyocarditis demonstrated JAK–STAT signaling was especially upregulated in myocarditis samples compared to unaffected controls. These findings support the potential beneficial effect of JAK–STAT inhibitor in irMyocarditis [28]. A theoretical issue of concern is the blockade of IFNγ signaling could potentially impair the antitumor immunity, which plays a crucial role in PD-1/PD-L1 responses [29–31]. However, it has been observed that sustained type I interferon signaling is associated with resistance to ICIs in cancer patients [32]. The combination of a JAK inhibitor with ICIs has been found to potentially overcome the immune resistance in preclinical models of non-small cell lung cancer and pancreatic cancer, independently of PD- L1 expression [33, 34]. This synergistic effect is thought to be the inhibition of JAK/STAT signaling will induce a favorable immunomodulation of the inflammatory effects within the tumor microenvironment induced by ICI treatment [35].

The use of tofacitinib for the management of irAEs has been previously reported in case series with promising results, including patients with ICI-colitis and irMyocarditis without impeding immune surveillance against cancer [17, 18, 36]. In our study, the most common indication for tofacitinib treatment was irMyocarditis, accounting for 46 out of 53 patients (86.8%). Additionally, 7 patients required tofacitinib for the management of other irAEs, including hepatitis (n = 2, Fig. S1), pneumonitis (n = 2, Fig. S2), and dermatomyositis (n = 3). Patients in this study were further divided into 3 groups stratified by the clinical severity and steroid responsiveness. Compared with steroid resistance group and steroid taper failure group, life-threatening cases had a higher percentage of multi-organ involvement, received higher initial doses of steroid and experienced earlier initiation of tofacitinib administration. Noteworthy, a shorter course of steroid treatment was observed possibly due to the poor prognosis in fulminant cases. Clinical remission was achieved in 6 out of 11 patients (54.5%) who received tofacitinib for the treatment of severe irAEs. However, it should be acknowledged that potential confounding effect may exist, as life-threatening cases often received high-dose corticosteroids in conjunction with multiple other immunosuppressive agents. Therefore, further robust evidence is required to demonstrate the efficacy of tofacitinib specifically in the treatment of fulminant irAE cases. Indeed, a recent study by Salem has demonstrated a strategy utilizing a combination of CTLA-4 agonist abatacept and JAK–STAT inhibitor ruxolitinib, along with corticosteroids, could effectively reduce the fatality rate in patients with severe irMyocarditis [28], suggesting that a single immunosuppressive agent may not be sufficient to

effectively manage cases with irAEs in critical condition. For cases that are steroid non-responders, the introduction of tofacitinib led to a rapid decrease in cTnT levels with clinical improvement in patients with irMyocarditis. This provides compelling evidence for the clinical significance of tofacitinib in the treatment of steroid-resistant irAEs. Among the 12 patients who experienced steroid taper failure, they had a longer duration of steroid treatment and tofacitinib administration, but all achieved clinical remission during the follow-up. When patients experienced relapse during steroid tapering, the subsequent use of tofacitinib led to a gradual decline in cTnT levels. These findings validate the efficacy of tofacitinib as an additional immunosuppressive therapy for patients with irAEs, particular in the context of irMyocarditis.

There have been concerns regarding the potential increased risk of infection and venous thromboembolism associated with tofacitinib treatment [37, 38]. Infectious adverse events were only observed in 4 patients (7.5%) without thromboembolic events observed in this cohort, suggesting an acceptable toxicity during steroid and tofacitinib combination therapy in cancer patients. Of note, cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis has also been reported in large phase III clinical trials [39, 40]. However, this might not be the case for patients receiving tofacitinib for irAE treatment in this cohort, which involves shorter term and lower dosage used of tofacitinib treatment and limited survival time for advanced cancer patients compared to patients with rheumatoid arthritis. These factors contribute to a different safety profile in the context of tofacitinib treatment for irAEs.

Still, a major concern is the sparsity of data regarding the efficacy of glucocorticoids and tofacitinib on anticancer responses for irAEs treatment. In this study, 48 patients (92.5%) had stage IV tumors, and the other 5 had stage III tumors. The median duration of steroid therapy and tofacitinib treatment was 71.5 days and 48.5 days, respectively. The median OS in our cohort was 16.1 months, which represent an average time for late-stage cancer patients. Noteworthy, even though patients in steroid taper failure group experienced longer duration of steroid and tofacitinib, the median OS reached 22.8 months, suggesting that tofacitinib treatment may not impair the antitumor activity of ICIs. However, it is important to note that our cohort consisted of patients with various cancer types that were treated by different ICI regimens. The heterogeneity of our cohort limited the ability to draw any solid conclusions from this result.

The limitations of this study include the retrospective nature of our analysis limits the robustness of the findings and introduces potential biases. Additionally, we included a broad spectrum of ICI regimens and cancer types with a relatively small sample size of patients, which may have skewed outcomes. Moreover, the lack of a standardized definition for life-threatening, steroid-resistant, or steroid taper failure irAEs poses challenges in accurately categorizing certain patients. We also admit that a large proportion of patients treated in this cohort are with refractory myocarditis/myositis, and the variations in dosages of tofacitinib treatment could potentially influence the efficacy of tofacitinib in managing irAEs. Nonetheless, it is important to highlight that this study represents the largest clinical cohort to date, providing valuable insights into the use of tofacitinib for the treatment of irAEs. Given its oral route of administration with fast onset and short half-life, tofacitinib is a promising therapeutic option that warrants further investigation in carefully designed clinical trials for the treatment of irAEs. Noteworthy, this treatment approach underscores the need for a standardized system that is tailored to the clinical severity and steroid sensitivity of irAEs induced by ICIs.

Conclusions

In summary, tofacitinib showed promising clinical efficacy in 47 of 53 patients experiencing irAEs, particularly in patients who had steroid resistance or experienced failure during steroid tapering. Moreover, and most importantly, tofacitinib exhibited a favorable safety profile in cancer patients developing irAEs in terms of both toxicity and anti-tumor activity. Future well-designed prospective studies are warranted to further evaluate the feasibility and efficacy of this therapeutic strategy.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2. Figure 1. Changes in levels of total and direct bilirubin in the patientwith ICI-hepatitis. The patient presented a clinical profile indicative of icteric hepatitis related to ICI therapy. Abdominal MRI findings did not indicate any evidence of bile duct obstruction, while the results of liver histopathology suggested drug-induced hepatic injury. ST, steroid treatment; TT, tofacitinib treatment; PP, Plasmapheresis. Figure 2. Serial radiologic imaging in the patientwith ICI-pneumonitis. Pre-steroids: before steroids treatment initiation. Steroids taper, pre-tofacitinib: during steroids tapering and before additional tofacitinib treatment. Post-tofacitinib: after 4 weeks of additional tofacitinib treatment

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Author contributions
QL, MLL, ZZG, and TSL conceived, designed the study, and wrote the manuscript; QL, MLL, ZZG, JYL, NPZ, LZ, JHZ, HJZ, XZ, XDJ, and YYY were responsible for collecting the data; QL, MLL, ZZG, and YYY analyzed and visualized the data. All authors have read and approved the manuscript.

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Availability of data and materials
If the request is reasonable, the corresponding author can share the data from this study to the requestor.

Declarations

Ethics approval and consent to participate
This study has been approved by the Ethics Committee of Zhongshan Hospital affiliated to Fudan University (Approval No. B2023-178). All patients gave informed consent to participate in the study before taking part.

Competing interests
None declared.

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