Australasian Journal of Dermatology (2022) 63, 217–221 doi: 10.1111/ajd.13812

ORIGINAL RESEARCH

Thalidomide for prevention of camrelizumab-induced reactive cutaneous capillary endothelial proliferation

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ABSTRACT

Objectives: The study evaluated the efficacy of thalidomide in prevention of camrelizumab-induced reactive cutaneous capillary endothelial proliferation (RCCEP).

Methods: In this study, patients treated with camrelizumab plus thalidomide or camrelizumab alone were included. The occurrences, onset time, severity of RCCEP and the adverse effect of thalidomide were analysed.

Results: A total of 19 patients were enrolled. The incidence of RCCEP in thalidomide group (2/9, 22.2%) was significantly lower than that in camrelizumab group (8/10, 80%). The median onset time of RCCEP was 5 weeks and 4 weeks respectively. The adverse events of thalidomide were mild, and no treatment-associated interruption was observed.

Conclusions: Thalidomide showed a promising in prevention of the RCCEP in patients receiving camrelizumab therapy with an acceptable safety profile.

Key words: camrelizumab, reactive cutaneous capillary endothelial proliferation, thalidomide.

ABBREVIATIONS

INTRODUCTION

Immune checkpoint inhibitors (ICIs) which include a novel class of monoclonal antibodies targeting the checkpoints, such as programmed cell death-1 (PD-1), PD-1 ligand (PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), have been approved by FDA and China National Medical Products Administration (NMPA) as notable new treatments for many kinds of malignant tumours.[1–3] Blockade of the interaction of PD-1 and PD-L1, which is the critical mediator of tumour-induced immune suppression, can lead to the activation of antitumor effection.[4] ICIs' overall safety seems satisfactory; however, the uncontrolled immune activation can also cause tissue damage, namely ICI-related toxicity or immune-related adverse events (irAEs). Due to the differences in selected agents, dosage and disease settings, the reported incidences of any-grade irAEs related to ICIs ranges from 15% to 90%.[5–7] The skin, liver, endocrine, gut and lung irAEs occur commonly, whereas hematologic, neurologic and cardiovascular ICI-related complications are relatively less frequent.[8] The characteristics of skin irAEs are different from the dermatologic adverse effects induced by chemotherapy drugs and targeted therapy agents.[9]

CTLA-4cytotoxic T-lymphocyte-associated antigen-4ESCCoesophageal squamous cell carcinomaHCChepatocellular carcinomaHLHodgkin lymphomaICIImmune checkpoint inhibitorsirAEsimmune-related adverse eventsNMPANational Medical Products AdministrationPD-1programmed cell death-1RCCEPreactive cutaneous capillary endothelial proliferationVEGFvascular endothelial growth factor

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Funding: This research was supported by the National Natural Science Foundation of China (No. 81872504).

Conflict of Interest: The authors declare no potential conflicts of interest.

Authors' Contributions: Huai-Dong Cheng and Geng Song contributed to the conception of the study. Geng Song and Fei-Fei Zhang performed the experiment and data analyses. Geng Song wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Ethical Approval: The open-label randomised controlled trial was conducted at department of oncology in the second affiliated hospital of Anhui Medical University, approved by the local ethic committees of the second affiliated hospital of Anhui Medical University (Number of Ethical Approval: 2012088) and followed good clinical practice, local laws and regulations.

Consent to Participate: All participants were approved for trial enrolment by the investigators and provided their written informed consents before enrolling.

Consent for Publication: The manuscript is approved by all authors for publication. I would like to declare on behalf of the authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

Submitted 25 December 2021; revised 28 January 2022; accepted 8 February 2022.

Camrelizumab is a PD-1 inhibitor developed by Jiangsu Hengrui Medicine Co., Ltd. Compared with the others irAEs, such as immune-related pneumonitis and colitis, the incidence of reactive cutaneous capillary endothelial proliferation (RCCEP) caused by camrelizumab is obviously high. Studies showed that incidences of RCCEP ranged from 60% to 90%.[10,11] Although most RCCEP are mild to moderate in severity, a few serious Grade 3 to 4 RCCEP can bring about temporary or permanent discontinuation of treatment and life-threatening complications. The exact mechanism that underpins the development of RCCEP remains to be fully established. Through binding to vascular endothelial growth factor (VEGF), camrelizumab could drive development of capillary hyperplasia. Lesions display high expression of VEGF-A, which might explain the mechanism of RCCEP to some extent. The incidence of RCCEP in patients who received camrelizumab combined with anti-vascular agents were lower than that in patients with camrelizumab alone.[12] Thalidomide is an agent with antiangiogenic activity; however, in early 1960s, thalidomide was withdrawn from the market due to its serious teratogenic effects. Thalidomide has now re-emerged as a treatment of multiple myeloma, erythema nodosum leprosum, bleeding caused by gastrointestinal vascular malformation and chemotherapy-induced nausea and vomiting.[13–16] Since thalidomide has been proved to be an effective antiangiogenic drug in the treatment of malignant tumours, we hypothesised that it can decrease the incidence of RCCEP in patients who received camrelizumab therapy. To our knowledge, no studies had explored thalidomide as a therapy for RCCEP induced by camrelizumab; therefore, we conducted this study to evaluate the effection of thalidomide on RCCEP.

METHODS

Study design and participants

This open-label study was conducted at the department of oncology in the second affiliated hospital of Anhui Medical University, and was approved by local ethics committees. The study had two trial conditions: camrelizumab plus thalidomide *vs* camrelizumab alone. The study followed good clinical practice, local laws and regulations. All participants were approved for trial enrolment by the investigators and provided their written informed consents before enrolling.

All eligible patients were selected according to the following criteria: (i) at least 18 years of age, (ii) histologically or cytologically confirmed malignancies, (iii) naive to ICIs and scheduled to receive camrelizumab therapy, (iv) Karnofsky performance status (KPS) ≥ 70, (v) estimated life expectancy of 12 weeks or more and (vi) adequate organ function. Patients with the following characteristics were excluded: (i) clinically significant neuromuscular disorder, (ii) history of thrombosis, (iii) active, known or suspected autoimmune diseases and (iv) pregnancy must be excluded before start of thalidomide therapy. Preventing pregnancy thereafter by using of reliable method of contraception.

Procedures

We used simple randomisation with 1:1 allocation between two groups without masking. An independent research nurse received relevant training managed the randomisation and provided the computer-generated randomisation assignments. Patients were assigned to receive either camrelizumab therapy (camrelizumab 200 mg, intravenous drips, d1, every 3 weeks) or camrelizumab plus thalidomide (thalidomide 50 mg orally once daily) until confirmed disease progression, unacceptable toxicity, death and withdrawal of consent. Patients underwent entire skin inspection every 3 weeks while receiving therapy. We took photographs documenting the sites of skin lesions prior to treatment in order to distinguish new lesions. The diagnosis of RCCEP using history taking and physical examination was determined by two researchers together in order to improve the reliability. The clinical course of RCCEP was recorded.

Outcomes

The primary endpoints were incidences of RCCEP in thalidomide group and camrelizumab group. RCCEP was evaluated and graded by the oncologists or dermatologists. Severity of RCCEP was defined as follows: Grade 1: single or multiple nodules, the diameter of the largest nodule ≤10 mm, with or without rupture and bleeding; Grade 2: single or multiple nodules, the diameter of the largest nodule>10 mm, with or without rupture and bleeding; Grade 3: diffuse nodules, complicated with skin infection but not life-threatening, hospitalisation indicated; Grade 4: life-threatening diffuse nodules; Grade 5: death.[17] The second endpoint was the safety of the thalidomide. Adverse events were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE V4.0).[18]

Statistical analysis

Fisher exact test was used for statistical analysis. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS ver.17.0.

RESULTS

Patients

Between November 2019 and June 2021, a total of 23 patients were screened for eligibility, 19 of whom were randomly assigned to thalidomide group ($n = 9$) and camrelizumab alone group ($n = 10$). Four patients did not meet the inclusion criteria or met the exclusion criteria. The distributions of patients by age, gender and KPS were similar between two trial groups. The clinical baseline characteristics of the enrolled patients were shown in Table 1.

Efficacy

Two (2/9, 22.2%) patients in the thalidomide cohort and eight (8/10, 80%) patients in the camrelizumab cohort

Table 1 Baseline characteristics of treated patients

Characteristics	Thalidomide group (n = 9)	Camrelizumab group (n = 10)
Age, years	65.22 ± 15.15	60.20 ± 8.93
Gender, n (%)		
Male	6 (66.7%)	7 (70%)
Female	3 (33.3%)	3 (30%)
KPS	82.22 ± 6.67	83.00 ± 6.75
Tumour types		
Hypopharynx squamous cell carcinoma	1	
Oesophageal squamous cell carcinoma	3	1
Hepatocellular carcinoma	1	
Intrahepatic cholangiocarcinoma	2	1
Endometrial carcinoma	1	
Cervical squamous cell carcinoma	1	
Gastric signet-ring cell carcinoma		1
Gastric adenocarcinoma		1
Lung squamous cell carcinoma		1
NK/T cell lymphoma		1
Rectal adenocarcinoma		2
Renal clear cell carcinoma		1
Ovarian serous carcinoma		1

KPS, Karnofsky performance status.

Table 2 Clinical features of RCCEP

Features	Thalidomide group (n = 9)	Camrelizumab group (n = 10)
RCCEP events n (%)	2 (22.2%)	8 (80%)
No. of camrelizumab injections, median (range)	4 (3 ~ 9)	4 (3 ~ 8)
Time on treatment, median (range), weeks	12 (9 ~ 27)	12 (9 ~ 24)
Time to onset, median (range), weeks	5 (4 ~ 6)	4 (3 ~ 6)
Severity n (%)		
Grade 1	1 (11.1%)	1 (10%)
Grade 2	1 (11.1%)	5 (50%)
Grade 3	0	2 (20%)
Grade 4 ~ 5	0	0

RCCEP, reactive cutaneous capillary endothelial proliferation.

developed RCCEP respectively. The two patients received thalidomide therapy had Grade 1 RCCEP, while among the eight patients in camrelizumab group, one (10%) patient had Grade 1 RCCEP, five (50%) patients had Grade 2 RCCEP, and two (20%) patients had Grade 3 RCCEP. The incidence of RCCEP in the thalidomide group was significantly lower than that in camrelizumab group (P = 0.023). The median time to onset of RCCEP was 5 weeks and 4 weeks in thalidomide and camrelizumab cohorts respectively. The median times on treatment on both groups were both 12 weeks. The clinical features of RCCEP are shown in Table 2.

Tolerability

The adverse events of thalidomide were analysed according to NCI-CTCAE V4.0. One patient experienced Grade 1 lower legs oedema, two patients experienced Grade 1 fatigue, and one patient experienced Grade 1 rash. No patients interrupted or terminated thalidomide treatment due to the adverse reactions.

DISCUSSION

Immunotherapy has revolutionised the treatment of solid tumours and haematological malignancies. PD-1/PD-L1 antibodies have been widely used in the treatments of various malignant tumours providing survival advantage.[19] As a humanised, high-affinity IgG4 monoclonal, anti-PD-1 antibody, camrelizumab has been conditionally approved by China NMPA in the treatments of advanced non-squamous non-small cell lung carcinoma, hepatocellular carcinoma (HCC), oesophageal squamous cell carcinoma (ESCC) and Hodgkin lymphoma (HL) as first-line or subsequent line therapies.[20–23] Despite camrelizumab's considerable potential for treating certain tumours, it still presented adverse effects caused by the non-specific activation of the immune system. The potential of camrelizumab for developing skin side effect appeared impressive. From the pembrolizumab, nivolumab and ipilimumab experiences, prevalent skin irAEs include rash, pruritus, alopecia, acne, vitiligo and exfoliative lesions, which were low-grade and manageable. Serious dermatologic irAEs included toxic epidermal necrolysis and Stevens–Johnson syndrome.[24] Except for the commonly reported skin irAEs, camrelizumab could induce a unique immune-related skin adverse effect, namely RCCEP. The pathogenesis of RCCEP has not been clearly defined. It was speculated that camrelizumab blocked the immunosuppression pathway, activated the immune response, promoted VEGF and thus induced benign skin capillary endothelial cell hyperplasia.[25] The incidence of RCCEP appeared to be broadly similar across different kinds of tumours. Studies of camrelizumab monotherapy showed that the incidence of RCCEP in patients with ESCC, HCC, HL and nasopharyngeal carcinoma were 76.7%, 66.8%, 87.3% and 88% respectively.[21–23]

According to the skin changes, RCCEP generally manifested with the following five types: 'red nevus type', 'pearl type', 'mulberry type', 'patch type' and 'tumour type', predominantly localised to the skin of the trunk, head and face. Most RCCEP occurred 2 ~ 4 weeks after the initial administration of camrelizumab. With the increasing cumulative dosage, the severity of RCCEP becmes higher. Most skin lesions would spontaneously atrophy and fall out 1 ~ 2 months after drug withdrawal.[26] Although most RCCEP were Grade 1 or 2 and did not lead to treatment discontinuation, RCCEP could cause cosmetic problems,

increase psychological distress and a few serious RCCEP might lead to life-threatening complications.

The management guidelines for RCCEP have not been established. The relationship between VEGF and susceptibility to RCCEP supports the use of inhibitors of VEGF in the treatment of RCCEP. Apatinib is a highly selective inhibitor directed to VEGF. Li and colleagues reported that eight lung cancer patients who received camrelizumab therapy had mild and moderate RCCEP and four patients achieved a regression of RCCEP after the use of apatinib.[27] In another study, the incidence of RCCEP in patients with advanced HCC, gastric cancer and gastroesophageal junction cancer treated with camrelizumab plus apatinib was only 12.1%.[28]

Although apatinib had been shown to be effective in RCCEP, the drug was too expensive for Chinese patients to be widely used. Furthermore, apatinib could lead to many side effects, such as hand–foot syndrome, hypertension, proteinuria and neutropenia, which might be the main reasons for limiting its application in RCCEP treatment. Thalidomide, as an antiangiogenic drug, played an important role in inhibition of VEGF mediated angiogenesis. We first explored the effection of thalidomide in prevention of RCCEP. In the study, the incidence of RCCEP in the camrelizumab group was 80% and the median onset time was 4 weeks, which were similar to the outcomes of the previous reports about camrelizumab.[11]The rate of RCCEP in thalidomide group was significantly lower than that in camrelizumab group. The combination of thalidomide reduced the occurrence of RCCEP effectively.

The recommended doses of thalidomide for multiple myeloma and cutaneous erythema nodosum leprosum ranged from 100 to 400 mg/day.[13,14] There was a lack of consensus on the dose and therapy duration of thalidomide in patients with other illnesses. Given the dose-dependent side effects of thalidomide, lower dosage of thalidomide might have an acceptable toxic profile. Low-dosage (50 mg/day) of thalidomide had been proved to be an effective treatment for hereditary haemorrhagic telangiectasia and crohn's disease with mild adverse effects.[29,30] With regards to our study, it was observed to have a dramatic decline in the incidence of RCCEP with a dose of 50 mg/day in thalidomide therapy. The side effects were grade 1 lower legs oedema, fatigue and rash.

There were some limitations to the study. First, the sample size was small. Only 19 patients were enrolled in the study. Second, the study was not blinded to the assessors. Further larger sample randomised controlled study will be needed in future. In summary, the study is the first work to show that the addition of thalidomide looks promising for prevention the RCCEP in patients received camrelizumab therapy with a manageable safety profile.

ACKNOWLEDGEMENTS

This research was supported by the National Natural Science Foundation of China (No. 81872504). We thank all the patients and the institution for supporting the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of the study are available from the corresponding author upon reasonable request.

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