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Comparison of Thalidomide Versus Apatinib for Prevention of Camrelizumab-Induced Reactive Cutaneous Capillary Endothelial Proliferation

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Abstract

Objectives: We evaluated the effect of thalidomide and apatinib in prevention of camrelizumab-induced Reactive Cutaneous Capillary Endothelial Proliferation (RCCEP).

Methods: In this study, patients were randomly assigned (1:1) to either camrelizumab plus thalidomide therapy (thalidomide group) or camrelizumab plus apatinib therapy (apatinib group). The incidences of RCCEP and the adverse events of thalidomide and apatinib were analyzed.

Results: Between October 2020 and June 2022, 30 patients were enrolled. Although the incidence of RCCEP in thalidomide group (4/15, 26.7%) was lower than that in apatinib group (6/15, 40%), the significance threshold was not met (p=0.45). The adverse events of thalidomide included fatigue, constipation and rash which were mild in severity and manageable, and no treatment-associated interruptions were observed.

Conclusions: Compared with apatinib, thalidomide exhibits a trend towards better prevention of RCCEP with an acceptable tolerance in patients receiving camrelizumab treatment.

Keywords: Thalidomide; Apatinib; Camrelizumab; Reactive cutaneous capillary endothelial proliferation.

Introduction

Since the using of anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4) in the treatment of melanoma, the immune checkpoint inhibitors (ICIs) had achieved many impressive successes in the field of cancer immunotherapy. The antibodies against programmed cell death 1 (PD-1) and its ligand (PD-L1) had brought patients with durable responses and extension of survival [1]. The PD-1 and PD-L1 inhibitors upregulated the anti-tumor activation of T cells, however, the agents also caused autoimmune inflammatory termed immune-related adverse events (irAEs). IrAEs often involved the organs like skin, thyroid, lung, gut and liver [2]. Rash, pruritus and vitiligo were some of the most frequently occured skin irAEs and the incidences of these all-grade cutaneous adverse events ranged from 8%～20% [3].

Camrelizumab was an antibody against PD-1 developed by Jiangsu Hengrui Medicine Co.,Ltd. Except for the common skin side effects, reactive cutaneous capillary endothelial proliferation (RCCEP) was a special irAE related to camrelizumab in the treat-

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ment of solid tumors [4,5]. The diffuse lesions of RCCEP might cause severe bleeding and infection, however, there was no standard protocol for RCCEP to date. As an anti-angiogenic agent, apatinib had been used to treat RCCEP [6], however, the high price and kinds of adverse effects limited its use [7]. As our previous study had shown that thalidomide is effective for prevention the RCCEP [8], hence, we prospectively conducted the randomized controlled trial to compare the clinical benefits of thalidomide and apatinib in prevention the RCCEP in patients receiving camrelizumab therapy.

Method

Study design and participants

The unblinded, randomized controlled study was conducted in the department of oncology of the second affiliated hospital of Anhui Medical University. The study was approved by the ethics committee of the second affiliated hospital of Anhui Medical University (Number of Ethical Approval: 2012088) and followed good clinical practice, local laws and regulations. All participants provided their written informed consents before enrolment.

Eligible patients were 18 years or older, with histologically or cytologically confirmed malignant tumors and had Karnofsky performance status (KPS)≥70. Patients also had to have adequate bone marrow, liver, renal and cardiac functions. Key exclusion criteria were previous treatment with camrelizumab or apatinib, active or history of autoimmune disease, history of thrombosis, pregnancy and uncontrolled blood pressure or proteinuria.

Procedures

We used simple randomization with 1:1 assignment between two groups. The procedures of computer-generated randomized allocation were conducted by an independent research nurse who did not participate in the implementation of the study. Patients were randomly assigned to either camrelizumab plus thalidomide (camrelizumab 200 mg, intravenous drips, d1, every 3 weeks and thalidomide 50 mg orally once daily) or camrelizumab combined with apatinib (camrelizumab 200 mg, intravenous drips, d1, every 3 weeks and apatinib 250 mg orally once daily) until intolerable adverse events, confirmed disease progression, death or withdrawal of consent. A thorough examination of the entire skin was performed at each visit. The already existed skin lesions (such as cherry angiomas) prior to camrelizumab therapy and new lesions were recorded by photographs. Because RCCEP was a special irAE related to camrelizumab with relatively different morphological manifestations, the occurrences of new skin lesions during treatment could be identified as RCCEP. Two researchers made the diagnosis of RCCEP together, and we could consult dermatologists when the diagnosis was uncertain.

Outcomes

The primary endpoints were incidences of RCCEP in thalidomide group and apatinib group. RCCEP were diagnosed and graded by the oncologists or dermatologists objectively. We defined severity of RCCEP according to the following criteria: 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, hospitalization indicated; Grade 4: life-threatening diffuse nodules; Grade 5: death [9]. The second endpoint were the safeties of thalidomide and apatinib. The adverse events were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE V4.0) [10].

Statistical analysis

Fisher exact test was used to assess whether the incidence of RCCEP was significantly different between the thalidomide group and apatinib group. A two-sided $p<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS ver.17.0.

Results

Between October 2020 and June 2022, in total, 35 patients with malignant tumors consented to participate, of whom 32 patients were enrolled and randomly assigned to thalidomide group (n=15) or apatinib group (n=15). Two patients in the thalidomide group and apatinib group discontinued treatment before the first scheduled post-baseline skin examination, therefore, 30 patients were evaluable. No significant differences in demographic information, including age, gender and KPS existed at the baseline (Table 1).

Efficacy

The incidences of RCCEP in thalidomide cohort and apatinib cohort were 26.7% (4/15) and 40% (6/15), respectively. Although the incidence of RCCEP in thalidomide group was lower than that in apatinib group, the significance threshold was not met (p=0.45). The incidences of Grade 1 RCCEP were similar in thalidomide group (3/15, 20%) and apatinib group (4/15, 26.7%), while in patients received thalidomide treatment only one patient (6.7%) had Grade 2 RCCEP and in apatinib group there were 2 cases (13.3%) with Grade 2 RCCEP. The median time of onset of RCCEP were both 4 weeks in two groups. The characteristics of RCCEP were shown in Table 2.

Tolerability

Thalidomide and apatinib resulted in completely different spectrum of adverse reactions and no Grade 3 or higher adverse reactions were observed in thalidomide group (Table 3). In thalidomide group, there were 4 (26.7%) patients experienced Grade 1 fatigue, 3 (20%) patients experienced constipation (2 patients Grade 2 and one patient Grade 1) and 1 patients developed Grade 1 rash. In apatinib group, the most common adverse events was hypertension (6/15, 40%, 5 patients Grade 2 and 1 patients Grade 3), other adverse events included proteinuria (4/15, 26.7%, 3 patients Grade 1 and one patients Grade 2), hand-foot skin reaction (3/15, 20%, 2 patients Grade 1 and one patients Grade 2), neutropenia (2/15, 13.3%, Grade 1), diarrhea (2/15, 13.3%, Grade 1), elevated transaminase (2/15, 13.3%, Grade 1) and thrombocytopenia (1/15, 6.7%, Grade 1). The patients who developed adverse events were treated symptomatically and none stopped or interrupted therapy due to side effects.

Table 1: Baseline characteristics of treated patients.

Characteristics	Thalidomide group (n=15)	Apatinib group (n=15)
Age,years	66.5 ± 13.04	65.1 ± 7.63
Gender, n(%)		
Male	12 (80%)	12 (80%)
Female	3 (20%)	3 (20%)
KPS	82 ± 5.41	80 ± 5.16
Tumor types, n(%)		
Gastric carcinoma	6 (40%)	9 (60%)
Esophageal carcinoma	4 (26.7%)	4 (26.7%)
Others	5 (33.3%)	2 (13.3%)

KPS = Karnofsky Performance Status

Table 2: Characteristics of RCCEP.

Characteristics	Thalidomide group (n=15)	Apatinib group (n=15)
RCCEP events, n (%)	4 (26.7%)	6 (40%)
No of camrelizumab injections, median (range)	4 (2～8)	4 (3～8)
Onset time of RCCEP, median (range), weeks	4 (4～6)	4 (3～6)
Severity n (%)		
Grade 1	3 (20%)	4 (26.7%)
Grade 2	1 (6.7%)	2(13.3%)
Grade 3～5	0	0

RCCEP = reactive cutaneous capillary endothelial proliferation

Table 3: Occurrence of adverse events.

Adverse events, n(%)	Thalidomide group (n=15)	Apatinib group (n=15)
Fatigue	4 (26.7%)	
Constipation	3 (20%)	
Rash	2 (13.3%)	
Hypertension		6 (40%)
Proteinuria		4 (26.7%)
Hand-foot skin reaction		3 (20%)
Diarrhea		2 (13.3%)
Elevated transaminase		2(13.3%)
Neutropenia		2 (13.3%)
Thrombocytopenia		1 (6.7%)

Discussion

ICIs were relatively novel treatments for malignant tumors, but they also caused many kinds of irAEs which might impact the efficacy through dose-limiting toxicity [11]. Immune-related cutaneous toxicities were very common with a broad range of clinical manifestations which were different from the skin lesions induced by chemotherapy agents and targeted therapy agents in characteristics [12]. Camrelizumab was a humanized, anti-PD-1 antibody which had shown efficacy in many malignant tumors, however, the studies about camrelizumab all reported RCCEP as a novel toxicity. Most RCCEP were multiple and disseminated which could cause cosmetic-impairing and negative self-image evaluation. Unlike the other irAEs, RCCEP was insensitive to glucocorticoids. Hemostatics and antibiotics could be used for local bleeding and infection, and lesion excision or laser therapy could be given for uncontrolled hemostasis. The exploration of noninvasive treatments of RCCEP was necessary. As a highly selective VEGFR-2 antagonist, apatinib could inhibit the development of RCCEP [13], however, apatinib also have a high possibility of causing more adverse effects and financial problems. Thalidomide was commonly used as an antitumor drug with anti-angiogenic activity, so it also could be used to treat vascular proliferative diseases such as RCCEP via downregulation of VEGF [14].

The incidence and clinical course of RCCEP in thalidomide group were consistent with the results in our previous study [8]. Thalidomide therapy could reduce the incidence of RCCEP significantly and seemd to be more effective than apatinib. Accumulating studies showed that immunotherapy plus agents that inhibit VEGFR has displayed promising anti-tumor results in pathology-specific tumors which might not benefit from ICI monotherapy. As reported in the studies regarding camrelizumab in combination with apatinib therapy for biliary tract cancer, hepatocellular cancer, triple-negative breast cancer, gastroesophageal junction cancer and osteosarcoma, the incidences of RCCEP ranged from 30%～60% [15-19]. With the increasing of the apatinib dose and the prolonging of the apatinib course, the incidences of RCCEP were decreased. However, the incidence and severity of adverse events caused by apatinib increased in parallel with the dosage and course of apatinib. Among the patients in apatinib group in our study, hypertension, proteinuria and hand-foot skin reaction were the most common adverse events. The other adverse events included diarrhea, neutropenia and thrombocytopenia. The incidences of RCCEP and adverse events in apatinib group of our study were similar to the above studies.

As anti-angiogenesis kinase inhibitors, regorafenib and fruquintinib also blocked VEGFR-2 like apatinib, while Jiang et al[20] reported that 16 patients with colorectal cancer received regorafenib or fruquintinib plus camrelizumab therapy and the incidence of RCCEP was 81.3% which was obviously higher than thalidomide and apatnib. As an irAE, the exact underlying mechanism of RCCEP was not entire clear. According to the pathological features of RCCEP which showed hyperplastic capillaries with high expression of VEGF-A and VEGFR-2 in IHC staining [21], it was supposed that immune system activation may interfere with the balance of pro-angiogenic and anti-angiogenic factors. Compared with apatinib, regorafenib and fruquintinib, thalidomide might demonstrate greater immunomodulatory activity to successfully treat irAEs.

There was no consensus on the optimal dose and therapy duration of thalidomide in the treatment of vascular diseases. Our previous report demonstrated thalidomide response to a low dose 50 mg/day in prevention RCCEP, and this study supported the result that low dose thalidomide therapy was an effective option. The most common adverse effect was fatigue, followed by constipation and rash. All the toxicities were mild in severity and manageable.

The difference in patient baseline characteristics was that the proportion of gastric carcinoma patients in thalidomide group was lower than that in apatinib group, however, previous studies had shown the incidences of RCCEP are independent of tumor

types which range from 70%～80% in the patients with esophageal cancer, gastric cancer, hepatocellular cancer, colorectal cancer and nasopharyngeal cancer [4,18,22-24]. We thought that the difference of tumor proportion may not interfere with the result of the study.

We acknowledge that our study had several limitations. First, the main limitation was the small sample size which might not represent the actual differences between the two groups. Second, this was not a double-blind study and thus selection bias might reduce the certainty of results. Hence, it is necessary to recruit a larger number of patients in future randomized, double-blind controlled research to confirm the effectiveness of thalidomide therapy. In summary, a trend towards better prevention of RCCEP induced by camrelizumab was seen in thalidomide therapy, and the toxicities of thalidomide group seemd to be better tolerated than apatinib group.

Declarations

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Conflicts of interest: The authors declare no potential conflicts of interest.

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

Ethics approval: The open-label randomized 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 enrollment 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.

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