Salvage therapy of reactive capillary hemangiomas: Apatinib alleviates the unique adverse events induced by camrelizumab in non-small cell lung cancer

ABSTRACT

Background: Camrelizumab is a promising anti-programmed cell death-1 agent for non-small cell lung cancer (NSCLC) and induces reactive capillary hemangiomas (RCHs). Routine clinical management of this unique and prevalent toxicity has been summarized in previous studies. The objective of this study was to provide evidence of apatinib as a salvage therapy for RCHs.

Materials and Methods: In this single-center, observational study, patients with NSCLC who were over 18 years of age and treated with camrelizumab were enrolled. The incidence of RCHs, onset and duration time, severity, evolution, and clinical practices, especially with apatinib, for their management and impact on quality of life, were recorded during a 6-month follow-up.

Results: A total of 28 patients were included. The incidence of RCHs was 28.6% (8/28). The median onset and duration time were 6 weeks and 8 weeks, respectively. Six (21.4%) patients had mild and moderate RCHs and four (9.3%) patients achieved a rapid regression of RCHs with the application of apatinib. The impact of the RCHs on quality of life was limited and assessed with Dermatology Life Quality Index scores. No treatment-associated termination was observed.

Conclusion: The combination of camrelizumab and apatinib in the treatment of NSCLC reduced the incidence of RCHs. Apatinib appeared to be a salvage therapy of RCHs, which leads to rapid regression of RCHs with no impairment on the quality of life.

KEY WORDS: Apatinib, camrelizumab, non-small cell lung cancer, reactive capillary hemangiomas

INTRODUCTION

Immunotherapy targets checkpoint inhibitors. Targeted programmed cell death 1 (PD-1) axis inhibitors are widely used for the treatment of multiple solid tumors, especially non-small cell lung cancer (NSCLC).[1,2] Camrelizumab is a humanized, high-affinity IgG4 kappa monoclonal antibody against PD-1 that is produced by Hengrui Medicine (Jiangsu China) and has antitumor effects in multiple tumors.[3,4] Given the mechanism for triggering an imbalance in the immunological tolerance of anti-PD-1 treatment, camrelizumab can induce reactive capillary hemangiomas (RCHs), which is different from the adverse events occur in the skin induced by conventional systemic therapies. Compared with the toxicities of other adverse events such as gastrointestinal, pulmonary, endocrine, renal, and hepatic adverse effects, RCHs are unique toxicities and vary from time of onset and duration. Hence, the exploration of the evolution and efficient management of RCHs is necessary.

Finlay[5] reported that RCHs are highly specific off-target binding events. Camrelizumab, as a potent agonist of human vascular endothelial growth factor receptor 2 (VEGFR-2), mediates aberrant binding to VEGFR-2, thereby driving hemangioma development via vascular endothelial cell activation. Apatinib, as a VEGF-2 receptor antagonist, is applied to multiple solid tumors with clinical benefits.[6-10] Therefore, apatinib is proposed to be a salvage therapy for patients with RCHs due to the application of camrelizumab.

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However, currently, no studies have explored the evolution of RCHs and apatinib as a salvage therapy for RCHs induced by camrelizumab in NSCLC. Therefore, we conducted this study to explore the evolution of RCHs induced by camrelizumab in NSCLC and the effect of apatinib on RCHs.

**MATERIALS AND METHODS**

**Enrolled patients**

The eligibility criteria were as follows: age 18–85 years old, Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1, pathologically verified NSCLC, advanced stage, and adequate organ functions. Patients with hemangioma before the initiation of camrelizumab were excluded from the study. The other exclusion criteria included autoimmune disease, long-term application of hormone therapy, and antibiotic treatments during the previous 2 weeks. The study was approved by Shandong Provincial Hospital affiliated to Shandong First Medical University. All participants provided written informed consent.

**Camrelizumab administration**

Camrelizumab was administered intravenously at a dose of 200 mg on day 1, which was repeated every 2 weeks until intolerable adverse events or disease progression. For patients with disease progression but no symptom deterioration, camrelizumab administration was continued until confirmed disease progression.

**Apatinib administration**

Apatinib was administered orally at a dose of 250 mg once daily for patients with RCHs until total regression. For those who could not tolerate the toxicity, the dose of apatinib could be reduced to 250 mg once every 2 days. For patients treated with the combination of camrelizumab and apatinib, apatinib was administered orally at a dose of 250 mg once daily until intolerable toxicities or disease progression.

**Reactive capillary hemangiomas and other adverse events**

The adverse events of camrelizumab were evaluated according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.0.[11] RCHs were graded objectively by professional oncologists [Figures 1-4]. RCHs were classified based on skin changes that occupied the body surface area (BSA) and interfered with the activities of daily living (ADL). General characteristics of Common Terminology Criteria for Adverse Events grading is indicated as below: Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Grade 3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Grade 4 (Life threatening): Life-threatening consequences; urgent intervention indicated.

**Figure 1:** Evolution of patient 4 with RCHs, which appeared as mulberry-like lesions. (a) RCHs appeared on the temple accompanied with bleeding for the first time 1 month after camrelizumab. (b) RCHs regressed after application of apatinib for 2 weeks. (c) Histology performance: cluster-like proliferation of capillaries in dermis of skin tissue at 100 × magnification

**Figure 2:** Evolution of patient 6 with RCHs, which appeared as tumor-like lesions. (a) RCHs appeared for the first time on the little finger, accompanied by pain and bleeding 6 weeks after camrelizumab. (b) Histology performance: chronic inflammatory cell infiltration and hyperkeratosis of skin tissue at 100 × magnification. (c) RCHs regressed after application of apatinib for 2 weeks. (d) RCHs disappeared after application of apatinib for 1 month. (e) Nodular hyperplasia of collagen fiber, local granulation tissue can be seen at 100 × magnification
In a previous report, Wang et al.\textsuperscript{[12]} classified RCHs into five categories according to morphology: red nevus like, pearl like, mulberry like, plaque, and tumor like. The former two types are the most common. Multiple types can be observed in a patient and the type can change. The red nevus-like type increasing in size to pearl-like type and pearl-like type increasing in size to tumor-like type can be observed. Among patients with RCHs, we assessed the onset time, duration time, severity, evaluation, and outcome after apatinib interference [Table 1]. Other immune-related adverse events were also evaluated.

**Table 1: Reactive capillary hemangiomas and application of apatinib**

| Characters               | n (%) |
|--------------------------|-------|
| Incidence                |       |
| RCHs                     | 8 (28.6) |
| RCHs free                | 20 (71.4) |
| Appearance               |       |
| Red nevus like           | 2 (25.0) |
| Pearl like               | 2 (25.0) |
| Mulberry                 | 3 (37.5) |
| Tumor like               | 1 (12.5) |
| Grade                    |       |
| 1                        | 2 (25.0) |
| 2                        | 4 (50.0) |
| 3                        | 2 (25.0) |
| 4                        | 0 (0.0) |
| Onset time               |       |
| Median                   | 6.0 weeks |
| Range                    | 1.0 weeks-3.0 months |
| Onset time               |       |
| Median                   | 2.0 months |
| Range                    | 2.0 weeks-5.0 months |

RCHs=Reactive capillary hemangiomas

**Statistical analysis**

The statistical analyses were only descriptive due to the observational nature of the study. Qualitative numerical variables were presented as mean and range. Baseline characteristics, treatments, and therapeutic intervention of the patients who were biopsied for RCHs were recorded in detail.

**RESULTS**

**Characteristics of enrolled patients**

From November 1, 2018, to August 31, 2019, a total of 28 patients were enrolled. Among them, twenty patients (71.4%) were male and their mean age was 63.7 years (range from 29 to 82 years). Most patients were <75 years old (22, 78.6%). Twenty-two patients (78.6%) had an ECOG of 0. Camrelizumab was administered as a first-line therapy and subsequent line therapy in 5 (17.9%) and 23 patients (82.1%), respectively. Details of the enrolled patients are shown in Table 2.

**Reactive capillary hemangiomas**

Eight (28.6%) of the 28 patients developed RCHs. The clinical manifestations and details of patients with RCHs during the follow-up are described in detail in Tables 1 and 3. Among them, six patients had Grade 1 to 2 RCHs and two patients had Grade 3 RCHs. The median onset and duration time of RCHs were 6 weeks and 2 months, respectively. The pathology evolution was also recorded in two patients, which is shown in Figures 1 and 2.

**Apatinib intervention**

Four of the eight patients with RCHs were treated with apatinib. RCHs regressed 2 weeks after the administration...
of apatinib in all the four patients. The changes of RCHs before and after apatinib are shown for three patients in Figures 2-4.

**Other immune-related adverse events in patients with reactive capillary hemangiomas and camrelizumab discontinuation**

Immune-related pneumonia and hepatic dysfunction were the most common adverse events that were not RCHs [Table 3]. No patients terminated treatment as a result of the RCHs. However, two patients with Grade 3 immune-related pneumonia underwent treatment discontinuation. The delay of camrelizumab occurred in patients with hepatic dysfunction. The duration of treatment before discontinuation was 5 weeks. Patients with pneumonia were treated with prednisone and those with hepatic dysfunction were treated with hepatoprotective agents. All patients recovered after interventions, and no treatment-associated death was observed.

**DISCUSSION**

We first explored the evolution and pathological changes of RCHs in NSCLC patients treated with camrelizumab. Then, we explored the changes of RCHs after apatinib. RCHs were identified in 28.6% of patients. The median onset and duration time of RCHs were 6 weeks and 2 months, respectively. All RCHs regressed 2 weeks after intervention with apatinib. Those treated with camrelizumab more commonly developed RCHs than patients treated with camrelizumab and apatinib.

In this study, the incidence of RCHs was 28.6%, which is similar to other anti-PD-1 antibodies (e.g., nivolumab and pembrolizumab), but much lower than the outcome of a previous report. Perhaps, the difference was mainly due to the small sample. The onset time, duration time, and distribution of skin and membrane of RCHs induced by camrelizumab were also similar to previous studies.

RCHs exhibit a broad range of clinical appearances, such as maculopapular, follicular, pruritic, pustular, vesicular, acniform, and exfoliative lesions, which can be easily recognized based on the history of camrelizumab. Spontaneous regression is commonly observed in clinical practice. Interventions are generally not required, except in patients with a high risk of bleeding [plump or vulnerable lesions, such as patient 7, Figure 3]. Imiquimod 5% cream and oral corticosteroids (prednisone 1 mg/kg) are the main available treatments for the relief of RCHs. Topical corticosteroids and timolol hydrogen maleate also retard the growth of RCHs, but are not effective enough. Wounds subject to lesion excision heal completely and without recurrence; however, multiple sporadic distribution and invasion may limit the application.

RCHs are unique and prevalent cutaneous toxicities associated with camrelizumab. The exploration of a comprehensive and noninvasive therapy for the treatment of camrelizumab is necessary. Apatinib seems to be an available candidate as a salvage therapy. In this study, four patients with RCHs achieved rapid relief after the application of apatinib for only 2 weeks. According to Finlay, camrelizumab can mediate aberrant, but highly selective, low affinity binding to VEGFR2, frizzled class receptor 5, and UL16 binding protein 2, which may thereby drive hemangioma development via vascular endothelial cell activation. Apatinib is a VEGFR-2 antagonist and has been applied to multiple solid tumors and achieved clinical benefits. It can theoretically alleviate these kinds of prevalent adverse events based on Finlay’s research, and we also observed a similar outcome in our study.

There are several limitations to this study. First, we only enrolled 28 patients. Second, only four of the eight patients with RCHs were treated with apatinib. We will conduct a large sample study to explore the incidence of camrelizumab-associated RCHs and the effects of apatinib on RCHs in future. When this study was performed, there was no research that revealed the antitumor efficacy of the combination of anti-PD1 and apatinib, and we assessed the antitumor efficacy in our study. We will enroll more cases in future research and obtain molecular evidence of the association between RCHs and apatinib, thus assessing the role of apatinib in combination with camrelizumab in the treatment of pulmonary malignancy.

**CONCLUSION**

RCHs were common in NSCLC patients treated with camrelizumab. Apatinib may reduce the incidence and induce the rapid regression of RCHs.
Table 3: Clinical details of the eight patients with reactive capillary hemangiomas

| ID   | Appearance           | Distribution              | Grade | Onset | Duration | Other AEs                             | Therapy                          | Outcome                                      |
|------|----------------------|---------------------------|-------|-------|----------|---------------------------------------|-----------------------------------|----------------------------------------------|
| 1    | Red nevus-like       | Face, neck arms           | 2     | 1 week| 4 months | Pneumonia, hepatic dysfunction         | Prednisone, antibiotics,         | Partial regressed (1.5 months after camrelizumab) |
| 2    | Red nevus-like       | Neck, face                | 1     | 6 weeks| 4 months | No                                    | No                                | Partial regressed (2 months after camrelizumab) |
| 3    | Mulberry-like        | Cheek                     | 1     | 6 weeks| 2 months | No                                    | No                                | No                                            |
| 4    | Mulberry-like        | Forehead, neck temple     | 1     | 1 month| 2 months | No                                    | Apatinib                          | Partial regressed (at 6 weeks after camrelizumab) |
| 5    | Red nevus-like       | Torso, forehead, neck     | 1     | 3 months| 5 months | No                                    | No                                | No                                            |
| 6    | Tumor-like [Figure 2]| Torso, palpebral, conjunctiva, face, arms, pad of finger | 3     | 1.5 months| 2 months | No                                    | Disinfection antibiotics,         | Disappeared (at 1 month after apatinib)         |
| 7    | Pearl-like [Figure 3]| Neck, lip                 | 3     | 2 months| 1.5 months| No                                    | Apatinib                          | Disappeared (at 4 weeks after apatinib)         |
| 8    | Pearl-like, red nevus-like [Figure 4]| Torso, Forehead, neck arms, knuckle | 2     | 2 months| 2 weeks | Pneumonia                             | Apatinib                          | Disappeared (at 2 weeks after apatinib)         |

*Patients 4 and 6 with RCHs accepted biopsy of the rash on a voluntary basis, $^*$Patients 1 and 8 terminated delivery of camrelizumab due to immune-related pneumonia. AEs=Adverse events, RCHs=Reactive capillary hemangiomas

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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