Camrelizumab combined with microwave ablation improves the objective response rate in advanced non-small cell lung cancer

ABSTRACT

Aim: The present study evaluated the safety and efficacy of camrelizumab (a programmed death-1 antibody) in combination with microwave ablation (MWA) in advanced non-small cell lung cancer (NSCLC).

Materials and Methods: A total of 21 patients were prospectively enrolled. MWA was performed in 25 pulmonary lesions during 21 sessions. Camrelizumab was administered 5–7 days after MWA as a dose of 200 mg, which was repeated every 2 weeks until disease progression or intolerable toxicities. The primary endpoints were safety and the objective response rate (ORR). Other endpoints included progression-free survival (PFS) and overall survival (OS).

Results: The technical success rate was 100%. No treatment-associated deaths were identified. Major complications, minor complications, and side effects of MWA were observed in 9, 8, and 14 patients, respectively. The main major complications included pneumonia, hypothyroidism, pulmonary hemorrhage, and pleural effusion. The adverse events of camrelizumab included reactive skin capillary hyperplasia (n = 9), hypothyroidism (n = 5), pneumonia (n = 4), fatigue (n = 2), leukopenia (n = 1), and neutropenia (n = 1). Grade 2 and 3 camrelizumab adverse events were identified in eight and three patients, respectively. The ORR was 33.3%, with two patients achieving complete response and five patients achieving partial response. The median PFS was 5.1 months and OS was not reached.

Conclusions: Camrelizumab administration combined with MWA was safe in the treatment of advanced NSCLC, and the combination improved the ORR of camrelizumab alone compared to previous reports.

KEY WORDS: Camrelizumab, lung cancer, microwave ablation, objective response, progression-free survival, PD-1 antibody

INTRODUCTION

In China, lung cancer remains the leading cause of cancer-related morbidity and mortality. Non-small cell lung cancer (NSCLC) accounts for nearly 85% of lung cancers, primarily diagnosed at an advanced stage, losing the opportunity for radical surgery.[1] In advanced NSCLC patients without epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusion genes, the main treatment was previously chemotherapy.[2] Recently, immunotherapy targeting immune checkpoints, especially programmed death-1 (PD-1) or programmed death-ligand-1 (PD-L1), improved survival in advanced NSCLC, resulting in long-term survival becoming a reality.[3–7] Camrelizumab (AiRuiKa™) is a humanized high-affinity IgG4-kappa anti-PD-1 monoclonal antibody developed by Jiangsu Hengrui Medicine Co. Ltd. and indicated for the treatment of various malignancies.[8] However, the low response rate limited the applications of PD-1 antibodies.[9–11] Hence, the combination of PD-1 antibodies with other treatments was explored. The combination with chemotherapy or chemotherapy and targeted vascular endothelial growth factor receptor antibodies demonstrated survival advantage.[12] Moreover, PD-1 antibodies combined with irradiation improved survival. In a Phase II clinical trial in patients with oligometastases, pembrolizumab with irradiation at all tumor lesion sites demonstrated superior survival compared to pembrolizumab alone.[12] In addition, the PACIFIC trial reported that in locally advanced NSCLC unsuitable for surgery, concurrent chemoradiation

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followed by durvalumab indicated longer progression-free survival (PFS) compared to chemoradiation alone.[13]

Microwave ablation (MWA), as a thermal ablation method, is considered an alternative treatment in early-stage NSCLC contradicted to surgery or irradiation.[14,15] In case of advanced NSCLC, the combination of MWA and chemotherapy improved the PFS.[16,17] In patients with oligometastases or oligoprogression treated with EGFR-tyrosine kinase inhibitors, the survival advantage was dramatically significant.[18,19]

Furthermore, a previous study demonstrated that thermal ablation affects the immune function and PD-L1 expression in NSCLC. Treatment with MWA dramatically increased the proportion of CD8+ T cells and CD16+CD56+ natural killer (NK) cells. In concurrent colorectal carcinoma with oligometastatic liver metastases, when treated with radiofrequency ablation (RFA) in liver metastases, the primary tumors were biopsied preablation, followed by surgery postablation. The PD-L1 expression was upregulated in the postablation tumors compared to preablation tumors.[20] In addition, in breast tumor-bearing mice, the combination of PD-1 antibodies, CTLA-4 antibodies, and MWA indicated the best survival compared to MWA alone or immune therapy alone.[21] One case report confirmed that lesions previously treated with RFA shrank rapidly and dramatically compared to those untreated with RFA.[22]

To date, no study has explored the combination of MWA with PD-1 antibodies in the treatment of advanced NSCLC. Hence, this prospective study aimed to explore the safety and efficacy of MWA combined with camrelizumab.

MATERIALS AND METHODS

The inclusion and exclusion criteria
Patients with the following characteristics were prospectively enrolled in the study: (1) pathologically verified NSCLC, (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, (3) Stage IV or Stage IIIb or IIIc unfit for surgery, (4) at least one measurable tumor lesion other than the ablative lesions, (5) tumors located in the lung periphery, and (6) EGFR and ALK-negative mutations.

Patients with the following characteristics were excluded: (1) mixed NSCLC and small cell lung cancer (SCLC), (2) previous cancer during the past 5 years, (3) autoimmune diseases, (4) long-term hormone therapy, and (5) antibiotic treatments during the past 2 weeks.

Microwave ablation procedure
Under local anesthesia, MWA was performed at the primary and metastatic lung tumor sites. MWA was performed as previously described.[16,17] 5 gross glass opacity changed to ground glass opacity of 5–10 mm larger than the tumor edge was considered as technical success.

Camrelizumab administration
Following MWA, camrelizumab was administered after an interval of 5–7 days. Camrelizumab was administered intravenously at a dose of 200 mg, repeated every 2 weeks, and continued until disease progression or intolerable toxicities.

Microwave ablation complications
The complications of MWA were in accordance with the International Working Group on Image-Guided Tumor Ablation of the Society of Interventional Radiology. These complications were classified as major complications, minor complications, and side effects. A major complication refers to an event that leads to substantial morbidity and disability that increases the level of care, or results in hospital admission, or substantially lengthens the hospital stay. All other complications are considered as minor complications. Side effects are expected, undesirable consequences of the procedure that although occur commonly, rarely, or if ever, result in substantial morbidity. These include pain, the postablation syndrome, and asymptomatic pleural effusions and minimal asymptomatic perihepatic (or renal) fluid or blood collection seen during imaging.[23]

Adverse events with camrelizumab
The adverse events of camrelizumab were evaluated according to the common toxicity criteria 4.0. In patients with Grade 2 or more adverse events, camrelizumab administration was paused and glucocorticoid therapy was administered if necessary.

The response to microwave ablation and camrelizumab
Contrast-enhanced computed tomography was conducted 1 month post-MWA during the first three months and every 2 months during camrelizumab treatment for a period of 2 years and every 3 months thereafter.

The response to MWA was evaluated according to the expert consensus for the thermal ablation of primary and metastatic lung tumors (2018 edition), classified as complete ablation and incomplete ablation.[24]

The response to camrelizumab was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which included complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD).[25]

The objective response rate (ORR) is defined as the proportion of patients who achieved CR and PR. Disease control rate (DCR) is the proportion of patients who achieved CR and PR, and SD newer lesions occurring during camrelizumab treatment were reevaluated 2 months later. Patients could continue camrelizumab treatment when the image evaluated the PD and patients did not display worsening symptoms.

Statistical analysis
All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The PFS was
calculated from the date of MWA to disease progression or death. Overall survival (OS) was calculated from the date of MWA to death. Both PFS and OS were analyzed using the Kaplan–Meier method.

RESULTS

The characteristics of enrolled patients
A total of 21 patients were prospectively enrolled in the study. Among these patients, 13 patients were male, with a mean age of 64 years (ranging between 44 and 81). Most patients (11 patients) were current or previous smokers and had an ECOG of 1 (16 patients). Histologically, most patients demonstrated adenocarcinomas (n = 17), followed by squamous cell lung cancer (n = 3) and large cell lung cancer (n = 1). Eighteen patients were diagnosed with Stage IV cancer. EGFR and ALK were tested in all patients, with no EGFR-sensitive mutations or ALK fusion genes identified.

All patients were treated with MWA followed by camrelizumab. A total of 25 pulmonary tumor lesions were administered MWA during 21 procedures. The ablated tumors had a mean size of 3.4 cm (range: 1.4–7.9 cm). Most tumors were located in the right lung (n = 17) and upper or middle lobe (n = 16). The power applied was 40W, 50W, and 60W, with the mean ablative time of 13.4 min (range: 6–34 min). The details of enrolled patients and treatments are presented in Table 1.

The safety of microwave ablation combined with camrelizumab
All patients were treated with camrelizumab until the last follow-up conducted on October 30, 2019. Four median cycles of camrelizumab were performed (range: 1–14), with one patient treated with <4 cycles. Eleven patients indicated disease progression, and one fatality was noted.

The major complications, minor complications, and side effects were observed in 9, 8, and 14 patients, respectively. The main major complications included pneumothorax (n = 4), pneumonia (n = 4), hemorrhage (n = 3), and pleural effusion (n = 2). Chest tube insertions resolved the observed pneumothorax or pleural effusions, and the hemorrhage was observed in one patient. Three patients with pneumonia were administered anti-inflammatory therapy. Transbronchial artery interventional embolization was used to treat one patient with hemorrhage [Table 2].

The adverse events of camrelizumab as first or subsequent line treatment included reactive capillary endothelial proliferation (n = 9), hypothyroidism (n = 5), pneumonia (n = 4), fatigue (n = 2), leucopenia (n = 1), and neutropenia (n = 1). Grade 2 adverse events were identified in eight patients and Grade 3 adverse events were observed in three patients. Two patients with pneumonia discontinued treatment with camrelizumab and were treated with methylprednisolone and prednisone. After recovering from pneumonia, the two patients were rechallenged with camrelizumab; however, camrelizumab was terminated due to the occurrence of Grade 2 pneumonia [Table 3].
Objective response rate of camrelizumab combined with microwave ablation

Regarding the response to camrelizumab combined with MWA, CR was observed in two patients, PR was observed in five patients, and SD was observed in six patients [Figure 1]. The ORR was 33.3% and the DCR was 61.9%.

Overall survival with microwave ablation in combination with camrelizumab

With a median follow-up of 6 months, the median PFS was 5.1 months, ranging between 3.2 and 6.9 months. Death was reported in one patient, and the median OS was not reached.

DISCUSSION

In this study, we explored the combination of MWA and camrelizumab in advanced NSCLC, confirming that the combination was safe and improved the ORR.

PD-1 antibodies have been used extensively in the treatment of advanced NSCLC as first-line or subsequent therapies. The combination of PD-1 antibodies and the irradiation at all oligometastatic sites indicated survival advantage.

MWA, as a new thermal ablation method, has been indicated in the treatment of lung cancer. In addition, our previous prospective, randomized, controlled Phase III clinical trial confirmed that MWA in combination with chemotherapy improved both PFS and OS compared to chemotherapy alone as a first-line treatment in advanced NSCLC.

In this study, MWA combined with camrelizumab demonstrated superior ORR in first-line and subsequent treatments compared to previously reported data. However, the exact mechanism for this improvement remains unclear. We speculated that several reasons could be responsible for the observed results. First, studies have confirmed that oligometastatic NSCLC benefits from the combination of systemic and local treatments due to a reduction in tumor burden. Second, the immune reaction following treatment with MWA, particularly the immune function of CD8+ T cells and CD16+CD56+ NK cells, improved. Third, MWA and camrelizumab demonstrated synergistic effects. Previously, the transplanted tumor model of breast cancer indicated that MWA combined with the PD-1 and

| Table 2: Complications of microwave ablation |
|--------------------------------------------|
| **n (%)**                                  |
| Major complication                         |
| Pneumothorax                               | 4 (19.0) |
| Pneumonia                                  | 3 (14.3) |
| Hemorrhage                                 | 2 (9.5)  |
| Pleural effusion                           | 2 (9.5)  |
| Minor complication                         |
| Pneumothorax                               | 7 (33.3) |
| Subcutaneous emphysema                     | 1 (4.8)  |
| Side effects                               |
| Hemorrhage                                 | 12 (57.1)|
| Chest pain                                 | 6 (28.6) |
| Pleural effusion                           | 2 (9.5)  |
| Minor complications                        |
| Pneumothorax                               | 7 (33.3) |
| Subcutaneous emphysema                     | 1 (4.8)  |

| Table 3: Adverse events of camrelizumab     |
|---------------------------------------------|
| **n (%)**                                  |
| Reactive capillary hemangiomas              |
| Grade 1                                     | 5 (23.8) |
| Grade 2                                     | 4 (19.0) |
| Hypothyroidia                              |
| Grade 1                                     | 3 (14.3) |
| Grade 2                                     | 2 (9.5)  |
| Pneumonia                                  |
| Grade 2                                     | 3 (14.3) |
| Grade 3                                     | 1 (4.8)  |
| Fatigue                                    |
| Grade 1                                     | 2 (9.5)  |
| Leukopenia                                 |
| Grade 3                                     | 1 (4.8)  |
| Neutropenia                                |
| Grade 3                                     | 1 (4.8)  |

Figure 1: A 46-year-old female with Stage IV adenocarcinoma treated with camrelizumab and microwave ablation. (a-d) Multiple pulmonary metastases preablation. (e and f) Two lesions in the right lung were treated with microwave ablation. (g and h) Four months later, the lesions treated with microwave ablation became fibrotic scar. (i and j) Two months after administration of camrelizumab, the lesions disappeared and the response of immunotherapy was complete response.
CTLA-4 antibodies demonstrated a superior survival compared to the PD-1 antibody and CTLA-4 antibody or MWA alone.\textsuperscript{[21]}

The PFS was observed in previous studies and OS was not reached, indicating that the combination of camrelizumab and MWA was not inferior to the PD-1 antibody alone.

With regard to the safety, major complications of MWA were observed in nine patients and were resolved by intervention. The adverse events of camrelizumab included reactive capillary endothelial proliferation, hypothyroidism, pneumonia, fatigue, leukopenia, and neutropenia. Grade 3 adverse events were identified in three patients, as observed in previous reports. Notably, no treatment-associated deaths were observed.\textsuperscript{[20,21]}

This study had several limitations including the small sample size and limited follow-up dates. Furthermore, several patients received the PD-1 antibody for <3 cycles corrected to one patient received the PD-1 antibody for <4 cycles.

**CONCLUSIONS**

MWA combined with camrelizumab was safe and efficient in first-line and subsequent treatments of advanced NSCLC.

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Nil.

**Conflicts of interest**

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