Integrative Cancer Therapies
Volume 21: 1–11
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15347354221083968
journals.sagepub.com/home/ict
SAGE

A Single-Arm Phase II Study to Evaluate Efficacy and Safety of First-Line Treatment With DCVAC/LuCa, Standard of Care Chemotherapy and Shenqi Fuzheng Injection in Advanced (Stage IIIB/IV) Non-Small Cell Lung Cancer Patients

Qing Liu, MD[1*], Yanni Lou, MD[1*], Liya Li, MD[1], Guowang Yang, MD[2], Huijuan Cui, MD[1], Zhiqiang Cheng, MD[1], Yuan Li, MD[1], Meng Liu, MMed[1], Chao Deng, MD[1], Donggui Wan, MMed[1], Yongxia Yan, BM[3], and Liqun Jia, MD[1]

Abstract

Objectives: To evaluate the efficacy and safety of first-line treatment with a dendritic cell vaccination for lung cancer (DCVAC/LuCa), standard of care chemotherapy and Shenqi Fuzheng injection in patients with advanced (stage IIIB/IV) non-small cell lung cancer. **Patients and Methods:** Patients with histologically or cytologically confirmed recurrent metastatic or advanced NSCLC (stage IIIB/IV) with wild-type epidermal growth factor receptor (EGFR) or EGFR mutation which does not confer increased tumor susceptibility to EGFR-interacting drugs were recruited. For the treatment period, the first cycle of standard of care therapy (SoC) started 2 to 14 days after the leukapheresis procedure. SoC continued 4 to 6 cycles. DCVAC/LuCa was administered from the second cycle of SoC. DCVAC/LuCa was administered in a 3-week cycle schedule (5 doses) and then in a 6-week cycle schedule. Shenqi Fuzheng injection was administered 3 days before each DCVAC/LuCa administration for a total of 14 daily doses. Patients would undergo disease evaluation by computed tomography (CT) scan every 3 months. The primary and secondary endpoint was efficacy with regard to objective response rate (ORR) and progression free survival (PFS). The safety profile was measured by: incidence, type, and severity of all adverse events (AEs), laboratory abnormalities (blood routine test, urine test, and chemical test), physical status, and vital signs. Qi insufficiency was evaluated by tongue diagnosis and questionnaire survey with "Classification and Determination of constitution in TCM." **Results:** Twenty-three patients from 3 hospitals who received combination therapy were included. ORR was 34.8% (95% CI:16.4%-57.3%). Median duration of response was 5.51 m (95% CI:2.70-8.32). Median PFS was 10.72 m (95% CI:4.52-16.93), 1-year survival was 77.8%. mOS was 21.97 m (95% CI:13.68-30.25). There was 1 severe AE related to a history of heart disease and there were no adverse events related to DCVAC/LuCa treatment. Qi insufficiency was improved significantly ($P < .0001$) from 41.19 ± 14.58 before treatment to 10.52 ± 16.58 after treatment. **Conclusion:** DCVAC/LuCa, combined with standard of care chemotherapy and Shenqi Fuzheng injection exhibited good benefit in Chinese patients with recurrent metastatic or advanced (stage IIIB/IV) NSCLC, and also significantly improved Qi insufficiency constitution. There were no related adverse events with DCVAC/LuCa treatment.

Keywords
DCVAC/LuCa, chemotherapy, non-small cell lung cancer, Shenqi Fuzheng injection, first-line treatment

Submitted October 17, 2021; revised December 30, 2021; accepted February 11, 2022

Introduction

Lung cancer has remained the leading cause of cancer-related death in the world as well as in China for several decades, while among the common subtypes of lung cancer, non–small cell lung cancer (NSCLC) represents 85% of lung cancer cases.[1] An estimated 2.1 million new cases were diagnosed in 2018 (11.6% of the total).[2] Lung cancer is estimated to be responsible for nearly 1 in 5 deaths due to cancer (1.76 million deaths, 18.4% of the total). In China,

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

lung cancer ranks first in incidence rate and mortality rate.[3] The majority of patients are diagnosed with stage IIIB/IV NSCLC with disappointing 5-year survival rates of about 26% (stage IIIB) and 0% to 10% (stage IVA-IVB).[4] Thus, there is an urgent need to explore new treatment options to improve the outcome for patients with NSCLC.

The current guideline for the treatment of advanced-stage NSCLC recommends 4 to 6 cycles of platinum-based doublet chemotherapy in patients with a good performance status. Standard of care (SoC) therapy includes, but is not limited to, the following regimens: gemcitabine/cisplatin,[5] paclitaxel/carboplatin,[6] pemetrexed/carboplatin,[7] and pemetrexed/cisplatin.[8] Maintenance treatment of patients whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy can be done with pemetrexed monotherapy (until intolerance or disease progression).[9]

In light of recent advances in the understanding of the biology of the immune response and the importance of an anti-tumor immune response for long-term prognosis of cancer, immunotherapy has emerged as a novel modality in the treatment of cancer, is currently of high interest and is expected to improve outcomes of advanced NSCLC.[10] In this study a dendritic cell vaccination for lung cancer (DCVAC/LuCa), an immunotherapeutic product, was used. It consisted of autologous dendritic cells (DCs) differentiated from the patient's peripheral blood mononuclear cells (PBMCs) presenting tumor antigens derived from killed lung cancer cell lines. DCVAC has the ability to induce an immune response, including cytotoxic CD8+ T cells, against tumor-associated antigens expressed by patients' cancer cells. It is assumed that such an immune response might have an impact on the viability of the cancer cells and thereby prolong survival time.[11] SoC, which was viewed as immune-suppressive in the past, might in fact boost the anti-tumor responses.[12] Dendritic cell vaccination for prostate cancer (DCVAC/PCa) had shown that DC-based cancer immunotherapy is generally safe with very limited, and most often only low grade, adverse events (AEs).[11]

Multiple researchers have found that combining platinum-based chemotherapy with Chinese medicinal herbs (eg, Shenqi Fuzheng injection) for the treatment of advanced NSCLC may improve tumor response and performance status, as well as reduce chemotherapy toxicity.[13] The traditional Chinese medicine (TCM) tested in this study, Shenqi Fuzheng injection, concocted from 2 kinds of Chinese medicinal herbs: Huangqi (root of *Astragalus propinquus*) and Dangshen (root of Codonopsis pilosula), was approved by the State Food and Drug Administration of the People's Republic of China in 1999 (Drug Approval Number: Z19990065) primarily as an antitumor injection to be manufactured by Livzon Pharmaceutical Group Inc. (Zhuhai, Guangdong, China) and marketed in China.[14]

We hypothesize that immunization with DCVAC/LuCa administered to the patients in this study might induce the effector cells of the immune system to infiltrate tumors. The resulting immune reaction may lead to tumor mass reduction, prolongation of the time to disease progression, and, ultimately, to improved overall survival (OS). Shenqi Fuzheng injection has been widely used as an adjunctive therapy to chemotherapy in the treatment of lung cancer.[15] In addition, we hypothesize that the addition of Shenqi Fuzheng injection to DCVAC/LuCa and SoC may reduce the toxicity of SoC chemotherapy and enhance the anti-tumor immune responses generated by DCs loaded with tumor antigens and thus assist the immune system to overcome evasive strategies used by lung tumors.

Methods

Eligible Patients

This is a single-arm phase II clinical study implemented in China-Japan Friendship Hospital and Beijing Hospital of Traditional Chinese Medicine and Cixian Cancer Hospital. The inclusion criteria of patients in this study were 18 years of age or older; histologically or cytologically confirmed recurrent metastatic or advanced NSCLC (stage IIIB or IV) with wild-type epidermal growth factor receptor (EGFR) or EGFR mutation which does not confer increased tumor susceptibility to EGFR-interacting drugs; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients must have measurable disease as defined by RECIST v.1.1,[16] and be recovered from toxicity of any prior therapy (eg, surgery, radiotherapy, or therapy for other diseases than NSCLC). Recovery was defined as less than or equal to grade 2 toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (except alopecia).[17] All patients needed to have sufficient hematologic and organ function for leukapheresis and chemotherapy, signed informed consent form (ICF),

[1]China-Japan Friendship Hospital, Beijing, China
[2]Beijing Hospital of Traditional Chinese Medicine, Beijing, China
[3]Cixian Institute for Cancer Prevention and Control (Cixian Cancer Hospital), Cixian, Hebei Province, China

*These authors contributed equally to this work.

Corresponding Author:
Liqun Jia, Department of Integrative Oncology, China-Japan Friendship Hospital, No. 2 Yinghuayuan East Road, Chaoyang District, Beijing 100029, China.
Email: liqun-jia@hotmail.com

and ability to comply with the protocol. Positive result of testing of Qi insufficiency constitution score according to traditional Chinese medicine (TCM) guidelines (result: Yes) were required. If the result of testing showed a trend of yes (but no clear yes), the physician would perform tongue diagnostics according to TCM guidelines, and if this examination showed Qi insufficiency constitution, the patient was included in the study provided the other inclusion/exclusion criteria are fulfilled. Exclusion criteria included: (1) Known active/untreated central nervous system metastases. (2) Any known primary immunodeficiency. (3) Concurrent systematic radiotherapy for NSCLC. (4) Prior systemic treatment for metastatic or advanced NSCLC except neo-adjuvant or adjuvant therapy in association with the primary diagnosis of the cancer. (5) Any preexisting medical condition requiring long term chronic steroid or immunosuppressive therapy. (6) HIV positivity, hepatitis B and/or C infection, or active syphilis. (7) Past or current history of malignant neoplasm other than lung carcinoma, except for adequately treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years. (8) Patient significant co-morbidities: cardiovascular diseases and active severe infections or other severe medical condition. (9) Use of any experimental therapy, immunotherapy, or monoclonal antibodies within 4 weeks prior to the start of SoC. (10) Pregnant or breastfeeding woman. (11) History of severe hypersensitivity to the SoC intended for use in the individual patient and ingredients of this SoC, and/or to DCVAC/LuCa and its ingredients, and/or to TCM therapies and their ingredients. (12) Any contraindication to a component of the intended SoC therapy and/or TCM therapies according to the local prescription information or according to established documented local site standards.

Clinical Study Design

Ethics: The trial was performed with the approval of the Ethics Committee of China-Japan Friendship Hospital for Drug/Instrument Clinical Researches (2015-111). All patients signed an informed consent form before screening.

Each patient's participation in the study lasted until the end of the study and included the following study periods and treatments:

Screening period: Patients were screened for eligibility for the clinical study within a 4-week period.

Leukapheresis period: When the patients have been determined to meet all entry criteria, they would undergo leukapheresis as soon as possible. Within 2 to 14 days after the leukapheresis procedure (ie, after the start of production of the individual DCVAC/LuCa) and until the uneventful manufacturing process of DCVAC/LuCa for the individual patient, the patient would start treatment with SoC.

Manufacturing period: Manufacturing of DCVAC/LuCa is conducted under GMP conditions. Autologous peripheral blood mononuclear cells were obtained by leukapheresis. Adherent monocytes were selected and cultured in medium with IL-4 and GM-CSF. Killed cells from the lung cancer tumor cell lines H520 and H522 were prepared from working cell banks. Cells were cultured, treated with HHP, and frozen in aliquots of 20×10^6 cells per vial in 1 ml of freezing medium. HHP treated H520 and H522 cells were mixed in a ratio 1:1 and subsequently used for pulsing of DCs at a ratio of 5:1 of dendritic cells to tumor cells. DCs pulsed by the tumor cells were then matured by TLR-3 ligand (Poly(I:C)). The final product was then cryopreserved at a target of 1×10^7 dendritic cells per vial in 1 ml of freezing medium.

Treatment period: Patients were treated with the following:

SoC treatment: The first cycle of the selected (the Investigator's decision in the best interest of the patient and NSCLC histology) first-line SoC was started 2 to 14 days after the leukapheresis procedure per above. Investigators could choose from the following SoC regimens:

- paclitaxel (135-175 mg/m^2)/carboplatin (area under the curve [AUC] = 6 mg/ml per minute) administered on Day 1 of each 21-day cycle
- gemcitabine (1000-1250 mg/m^2)/cisplatin (75 mg/m^2) administered on Day 1 (gemcitabine also on Day 8) of each 21-day cycle
- pemetrexed (500 mg/m^2)/cisplatin (75 mg/m^2) administered on Day 1 of each 21-day cycle
- pemetrexed (500 mg/m^2)/carboplatin (AUC = 6 mg/ml per min up to a maximum of 900 mg) administered on Day 1 of each 21-day cycle

Patients with progressive disease would terminate SoC treatment but would be followed for survival. Patients with complete response, partial response, or stable disease continued SoC of combination chemotherapy for 4 to 6 cycles (target number of cycles; treatment might be stopped earlier due to patient intolerance).

Maintenance treatment of patients whose disease had not progressed after 4 cycles of platinum-based first-line chemotherapy could be done with pemetrexed monotherapy (500 mg/m^2, 3-week cycles until intolerance or disease progression).

In specific circumstances and if patient factors did not support the use of any of the above SoC regimens, it might be possible to use other medically acceptable first-line treatments for NSCLC provided the Collaborator and the treating physician both agree to it. Premedication for all drugs must be administered following the instruction on the package insert or according to established documented local site standards. Patients with intolerance to the selected

SoC doublet chemotherapy (not applicable to maintenance treatment with pemetrexed) could either be taken off the treatment or be switched to treatment with another alternative SoC per the list above. Alternatively, the SoC causing intolerance might be dose adjusted according to the prescription information for the components of the SoC, or according to established documented local site standards. Patients with intolerance to pemetrexed maintenance chemotherapy would discontinue pemetrexed.

If there was no intolerance suspected regarding DCVAC/LuCa or Shenqi Fuzheng injection, these treatments could continue irrespective of decisions regarding dose adjustments, termination, or switch of the SoC treatment. If there is a suspicion of intolerance to DCVAC/LuCa or Shenqi Fuzheng injection, the concerned treatment (or both treatments, if appropriate) should be stopped. In such a case, that is, when either or both DCVAC/LuCa and Shenqi Fuzheng injection were stopped for intolerance, the SoC, if not stopped earlier or at the same time due to intolerance, could be continued.

DCVAC/LuCa: DCVAC/LuCa was administered from the second cycle of SoC (on Day 15 [±2 days] of the SoC cycles). DCVAC/LuCa would initially be administered in a 3-week cycle schedule (5 times) and then in a 6-week cycle schedule (for the remainder of the treatment). Therefore, the first 5 doses of DCVAC/LuCa were administered 3 weeks apart, and subsequent doses were administered 6 weeks apart. If the SoC application was delayed for any reason, DCVAC/LuCa was administered at least 15 days (±2 days) after the last SoC administration (ie, SoC cycles are counted from Day 1 only when the SoC treatment actually starts on this day).

DCVAC/LuCa would be administered in up to a total of 15 doses, until development of intolerance to DCVAC/LuCa, or until there was a need to start new systemic anticancer therapy, regardless of concurrent SoC (ie, SoC might be stopped earlier or later than DCVAC/LuCa). It was assumed that the first leukapheresis would result in 10 to 15 doses of DCVAC/LuCa (ie, enough for 51-81 weeks of treatment with DCVAC/LuCa according to the study protocol). Therefore, the treatment with DCVAC/LuCa could be up to 15 doses, but 10 delivered doses would be acceptable at termination of DCVAC/LuCa treatment.

If available doses of DCVAC/LuCa from the first leukapheresis for an individual patient were foreseen not to be enough to continue treatment per above, a second leukapheresis could be done. In such a case, if maintenance pemetrexed was ongoing, 1 cycle of pemetrexed would be skipped and the second leukapheresis would be done at the end days of the skipped cycle (Day 17 to Day 19).

Shenqi Fuzheng injection: Shenqi Fuzheng injection (250 ml per day) were administered 3 days before each DCVAC/LuCa administration (when applicable, see below) and until a total of 14 daily doses had been administered. The Shenqi Fuzheng injection schedule was applicable during both 3-week and 6-week DCVAC/LuCa administration schedules. If DCVAC/LuCa was stopped before the administration of the SoC doublet chemotherapy was completed, Shenqi Fuzheng injection should be continued until the SoC doublet chemotherapy was terminated. Shenqi Fuzheng injection should be stopped in case of intolerance specifically attributed to Shenqi Fuzheng injection.

After completion of all doses of study treatment per protocol or treatment discontinuation for any reason, patients were evaluated at the End of Treatment (EoT) visit, which would be scheduled 30 days (+30 days) after the last dose of DCVAC/LuCa, chemotherapy, or Shenqi Fuzheng injection, whichever was later.

Follow-up periods: Patients who complete or discontinue all study treatments before disease progression would undergo disease evaluation by computed tomography (CT) scan every 3 months (±7 days) until progression of the disease or until 2 years after the start of SoC of the last patient.

Patients who completed or discontinued all study treatments after disease progression would be followed up for survival. The survival data was collected every 3 months (±7 days) by directly contacting the patient (or a relative/caretaker) by phone until death from any reason or until 2 years after the start of SoC of the last patient.

The clinical study would be terminated 2 years after the start of SoC of the last patient.

Measurement

Patients who completed or discontinued all study treatments before disease progression would undergo disease evaluation by computed tomography (CT) scan every 3 months (±7 days) until progression of the disease or until 2 years after the start of SoC of the last patient.

Efficacy endpoint: The primary and secondary endpoints were efficacy of Shenqi Fuzheng injection administered concurrently with DCVAC/LuCa plus SoC with regard to objective response rate (ORR) and progression free survival (PFS) according to RECIST v.1.1 in patients with recurrent metastatic or advanced (stage IIIB or IV) NSCLC and survival time as evaluated by 1-year survival rate, and overall survival (OS).

Safety endpoint: Safety profile of Shenqi Fuzheng injection administered concurrently with DCVAC/LuCa plus SoC as measured by adverse events (AEs), serious adverse events (SAEs), laboratory abnormalities, and clinical parameters (eg, performance status). Adverse events were graded according to NCI CTCAE4.03.

Qi insufficiency was measured in constitution from study baseline until maximum normalization on treatment as evaluated by tongue diagnosis and the Chinese medicine symptom score. The traditional Chinese constitution assessment was conducted by an independent chief

Table 1. Patients Characteristics.

Characteristic	Total number of patients (n = 23)
Age (median/range)	63.0 y/48.0-80 y
Gender (Male/Female)	19pts/4pts
ECOG status (0/1)	1pts/22pts
Stage (IIIB/IV)	7pts/15pts/1pt unknown
Histology (Adenomatous/Squamous cell/other)	16pts/5pts/1pt/1pt unidentified
EGFR mutation status (Wild type/mutation)	18pts/3pts

physician with rich experience in TCM clinical practice. If calculated score ≥40, it was Qi insufficiency constitution; calculated score = 30-39, it tended to be Qi deficiency constitution; calculated score <30, it was not Qi deficiency constitution.

Statistical Analysis

The modified intention to treat population (mITT) was consisted of all patients who had received at least 1 dose of the specified treatment, namely Shenqi Fuzheng injection, DCVAC/Luca or standard chemotherapy. Full analysis set (FAS) data set, total of 23, referred to all patients who had received at least 1 dose of specified treatment, namely Shenqi Fuzheng injection, DCVAC/LuCa plus SoC; Per protocol set (PPS) was composed of FAS data set who had received at least 3 doses of DCVAC/LuCa and whose curative effect could be evaluated without serious protocol violation. Kaplan Meier survival analysis was used to calculate and present PFS, OS, and DoR in chart form. Median remission and 95% CIs were obtained by Kaplan Meier survival analysis. Nonparametric testing was used to compare the calculated score of maximum improvement of Qi insufficiency before and after treatment. P values of $<.05$ were considered statistically significant.

Results

Patient Characteristics

Since December 2016 to November 2020, 23 eligible patients were enrolled in the study and followed up. Characteristics of patients are summarized in Table 1.

Therapeutic Regimen

Chemotherapy regimens applied in 23 patients were chosen according to investigator's decision in the best interest of the patient and NSCLC histology. Five patients received gemcitabine combined with platinum based systemic chemotherapy, 12 patients received pemetrexed combined with platinum chemotherapy and eight patients received paclitaxel combined with platinum chemotherapy. DCVAC/LuCa was administrated according to schematic design. The doses of DCVAC/LuCa ranged from 0 to 15 doses. Shenqi Fuzheng injection was administered 3 days before each DCVAC/LuCa administration until a total of 14 daily doses had been administered.

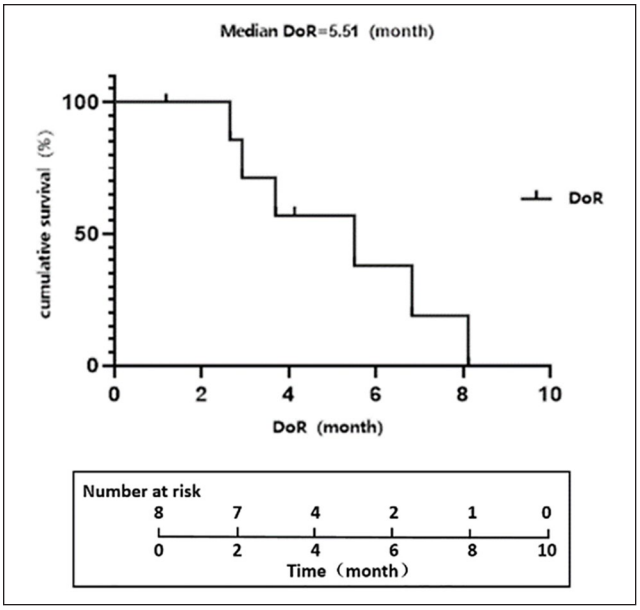

Figure 1. Survival curve of duration of response (DoR). The median DoR was 5.51 months.

Efficacy

From December 2016 to November 2020, 11 patients experienced PD and 10 patients died. One patient obtained CR and 7 patients experienced PR, ORR was 34.8% (95% CI:16.4%-57.3%). Median duration of response (DoR) was 5.51 m (95% CI:2.70-8.32), Median PFS was 10.72 m (95% CI:4.52-16.93), 1-year survival is currently 77.8%, mOS was 21.97 m (95% CI:13.68-30.25), as shown in Figures 1 and 2. The calculated score of maximum improvement of Qi insufficiency was improved significantly ($P < .0001$) from 41.19 ± 14.58 measured before treatment to 10.52 ± 16.58 measured after treatment (Table 2). Best tumor response compared with baseline in 23 patients is shown with a

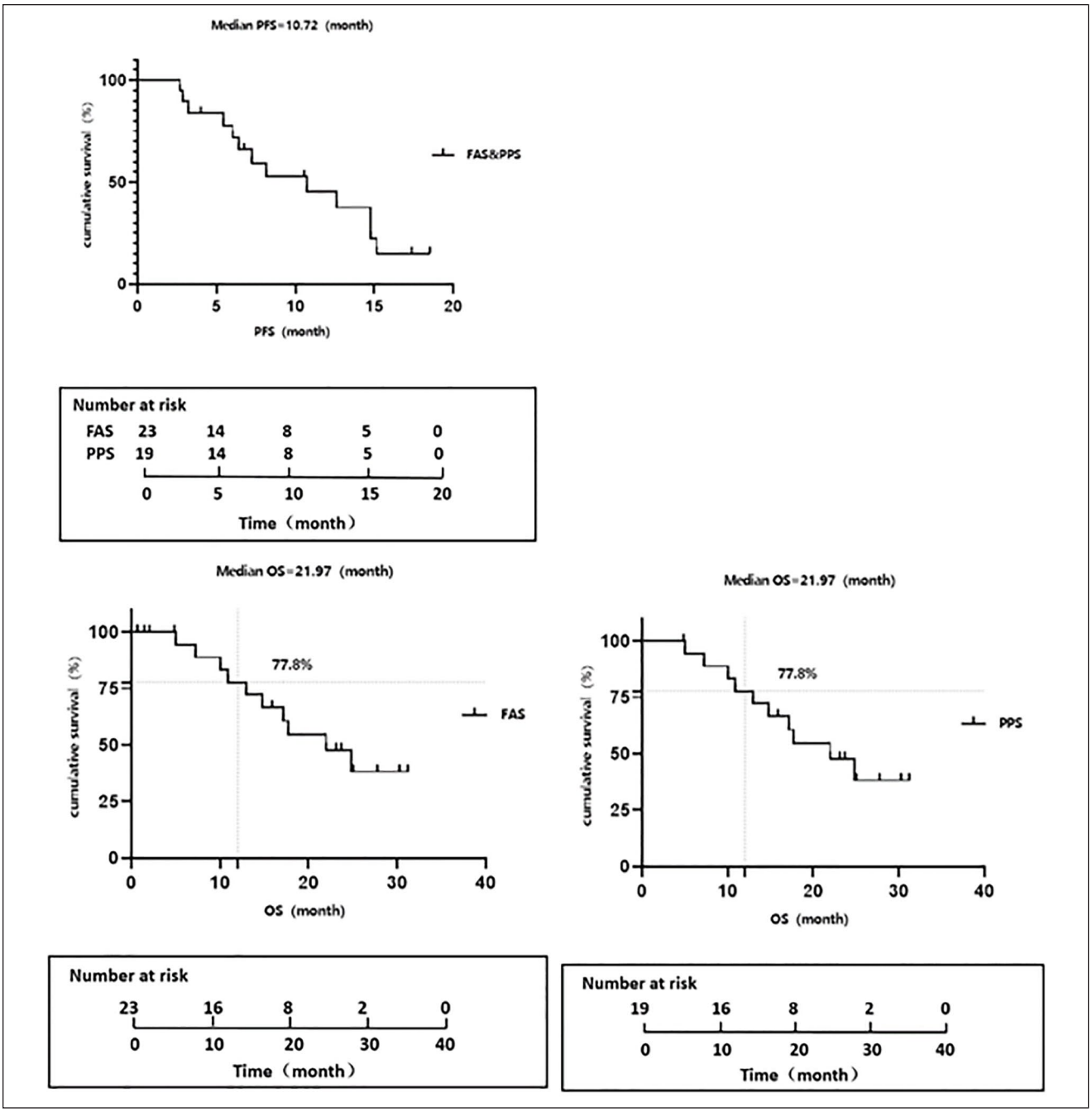

Figure 2. Kaplan–Meier survival curves of PFS and OS in patients of FAS and PPS set. The median PFS was 10.72 months, median OS was 21.97 m.

waterfall plot (Figure 3) and the relative changes in tumor size over time in all patients is shown with a spider plot (Figure 4).

Safety

The safety profile of Shenqi Fuzheng injection administered concurrently with DCVAC/LuCa plus SoC was recorded by incidence, type, and severity of all adverse events (AEs), serious adverse events (SAEs) and laboratory abnormalities.

Twenty-three patients were included in the safety profile. Fourteen (60.87%) patients had 79 AEs, and 10 (43.48%) patients had 34 adverse events related to chemotherapy. The most common reported (≥5%) AEs were increased alanine aminotransferase (13.04%), decreased

Table 2. Comparison of Maximum Improvement of Qi Deficiency Calculated Score Before and After Treatment.

Score	N (missing)	Before treatment Mean ± SD	Before treatment Median (interquartile range)	After treatment Mean ± SD	After treatment Median (interquartile range)	Nonparametric test	*P*-value
Raw score	22 (1)	21.18 ± 4.67	21 (21, 22)	10.55 ± 5.97	9 (8, 12)	$t = -9.37$	<.0001
Calculated score	22 (1)	41.19 ± 14.58	40.63 (40.6, 43.75)	10.52 ± 16.58	6.25 (0, 12.5)	$S = -115.50$	<.0001

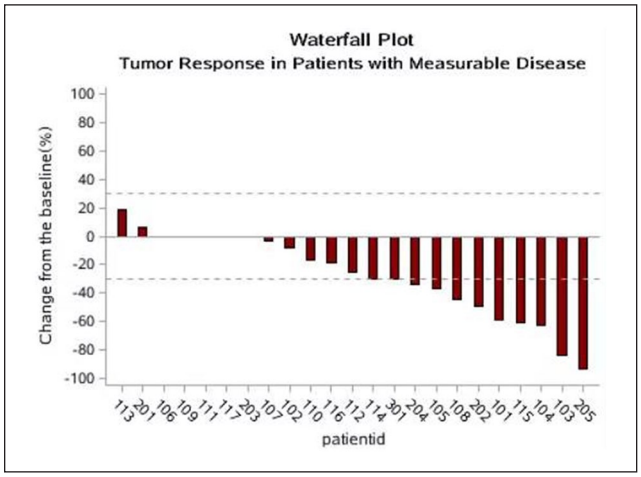

Figure 3. Best tumor response in 23 patients compared with baseline.

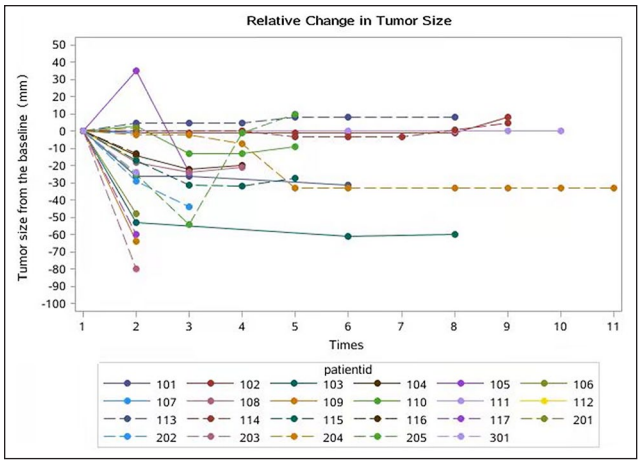

Figure 4. The relative changes in tumor size over time in all patients.

hemoglobin (13.04%), hemoptysis (13.04%), dyspnea (13.04%), fever (13.04%), fatigue (13.04%), palpitations (8.70%), decreased white blood cell count (8.70%), decreased platelet count (8.70%), nasopharyngitis (8.70%), and nausea (8.70%) (Table 3).

During the study period, no AE related to Shenqi Fuzheng Injection and DCVAC/Luca injection occurred. There were no adverse events in the analysis population of

Table 3. Adverse Events.

Preferred terms	n (%)
Increased alanine aminotransferase	3 (13.04)
Decreased hemoglobin	3 (13.04)
Hemoptysis	3 (13.04)
Dyspnea	3 (13.04)
Fever	3 (13.04)
Fatigue	3 (13.04)
Palpitations	2 (8.70)
Decreased white blood cell count	2 (8.70)
Decreased platelet count	2 (8.70)
Nasopharyngitis	2 (8.70)
Nausea	2 (8.70)

leukapheresis and within 24 hours after the start of leukapheresis. The severity of most AEs was mild to moderate (severity <3), 6 (26.09%) patients had 6 adverse events with severity ≥3, and there was no adverse reaction with severity ≥3 related to the study drug. There was no death due to AE and the outcome of most AE was remission (75.95%). A total of 10 subjects died and most (7 cases) of these were due to disease progression of lung cancer. There was one SAE related to medical history of heart disease reported and no serious adverse reactions related to the study drug reported.

Discussion

The primary goal of systemic therapy in patients with metastatic NSCLC is to reduce symptoms and improve survival, with a concurrent goal of improving quality of life. Active immunotherapies rely on specific stimulation of the host's immune system to trigger durable antitumor responses, which translate into a clinical benefit. Besides, immune response-mediated tumor eradication reduces the potential risks of toxicity and drug resistance.[18] Moreover, a great many studies related to immunotherapy combined with traditional anti-tumor strategies, including chemotherapy,[19] radiotherapy,[20] targeted therapy,[12] have shown the combination therapy is superior to monotherapy, and is worth further exploration.

Advanced NSCLC with a heavy tumor burden establishes a harsh landscape for immunotherapy due to immune tolerance toward tumor antigens. DC-based tumor

immunotherapies combined with chemotherapies are of potential interest in NSCLC. DCs have been documented as the most effective antigen-presenting cells that can activate primary and subsequent memory immune responses.[21] As initiators of adaptive immunity, DCs are ideal targets for ex vivo education and adoptive vaccination, which can induce specific antitumor immune responses in patients in vivo.[22]

DCVAC/LuCa is an active autologous cellular immunotherapy consisting of autologous DCs loaded with NSCLC antigens from NSCLC cell lines. DCVAC has the ability to induce an immune response, including cytotoxic CD8+ T cells, against tumor associated antigens expressed by patients' cancer cells.[23] It is assumed that such an immune response might have an impact on the viability of the cancer cells and thereby prolong survival time.

Recently results of a multicenter, parallel-group, randomized, phase I/II study (SLU01) in patients with histologically or cytologically confirmed stage IV unresectable NSCLC of adenomatous, squamous, or large cell carcinoma histology demonstrated a statistically significant effect of a DC-based immunotherapy in conjunction with platinum-based doublet on OS (15.5 vs 11.8 months; $P = .0179$; HR = 0.54; 95% CI:0.32-0.91) of all subpopulations (PP, male/female patients, smokers/former smokers, patients with squamous/non-squamous tumors) compared with chemotherapy alone. The differences of OS may be attributed to the characteristics of enrolled patients, as we included 86% of wild-type lung cancer and the majority was squamous NSCLC, while SLU01 might include some patients who would benefit from targeted therapy and had refractory lung cancer such as large cell cancer. In terms of safety, the results of both studies confirmed that DCVAC/LuCa was safe and well tolerated.[24]

Shenqi Fuzheng injection is composed of 2 kinds of Chinese medical herbs, huangqi and dangshen. The bioactive components of Shenqi Fuzheng injection include syringin, calycosin-7-O-β-D-glucopyranoside, lobetyolin, ononin, astragaloside IV, and others.[25] Shenqi Fuzheng injection showed good safety. Long-term toxicity testing in domestic rabbits showed no chronic toxic reactions after Shenqi Fuzheng injection was administered for 90 days. Among 20 100 patients observed, the incidence of adverse reactions was 1.85‰.[26] Increasing studies have shown that Shenqi Fuzheng injection has antineoplastic properties, including inhibiting cancer growth, promoting apoptosis, increasing chemotherapy sensitivity, and improving immune functions, etc.[27-30] Shenqi Fuzheng injection combined with chemotherapy would promote the levels of CD3+, CD4+, and CD4+/CD8+, thus effectively reduce the immunosuppression caused by chemotherapy.[31] Shenqi Fuzheng injection could improve quality of life and relieve Qi insufficiency symptoms such as shortness of breath, cough, and spontaneous perspiration as well as response rate to chemotherapy in NSCLC.[32,33]

A study had shown that patients with glioblastoma given tetanus toxoid has enhanced DC migration bilaterally and significantly improved survival.[34] It is evidenced that preconditioning with a potent recall antigen (eg, tetanus toxoid) enhances the antigenicity of immune cells, thus we assumed TCM may be another kind of recall antigen, and designed this clinical trial combining immunotherapy of DCVAC/LuCa and chemotherapy with adjuvant therapies of TCM to evaluate efficacy and safety. To our knowledge, the present trial is the first prospective open-label, multicenter, all-comers (male/female patients, smokers/former smokers, patients with squamous/non-squamous tumors), phase I/II study in patients with stage IV NSCLC, which combined TCM with DC-based tumor immunotherapy (DCVAC/LuCa). We can thus give a preliminary conclusion about the efficacy and safety of the combination.

In this study, in terms of effectiveness, the ORR of mITT population was 34.8% (95% CI 16.4%, 57.3%), the best overall remission rate was higher, and the treatment effect was better. The median remission period of mITT population was 5.5 m. The mPFS was 10.72 m (95% CI 4.52, 16.93), the one-year survival rate was 77.8%, mOS was 21.97 m (95% CI 13.68, 30.25). In the waterfall plot, we could clearly see the curative effect of 3 patients was very good, and the tumor was reduced by about 60%. Though the number of participants was relatively small, the survival outcome was better than those of advanced NSCLC patients receiving DCVAC/LuCa in combination with carboplatin and paclitaxel.[24]

The TCM Constitution of enrolled patients was evaluated by tongue examination and a constitution questionnaire survey with "Classification and Determination of constitution in TCM" which is an authoritative standard of the China Association of Chinese Medicine.[35] The tongue characteristic of Qi deficiency was light red in tongue body and tooth-marked in margins of the tongue. In addition, the symptoms were also important to describe Qi deficiency, such as low and weak pronunciation, short breath and laziness of speaking, fatigue, sweating easily, and lethargy. The standard of "Classification and Determination of constitution in TCM," published in 2009 is widely used in clinical and scientific research in China. This assessment was conducted by an independent chief physician with rich experience in TCM clinical practice. The results of the comparison of the raw score and calculated score of Qi insufficiency constitution score before and after treatment showed that the post-treatment score was significantly lower than that before treatment, and the evaluation of Qi insufficiency was significantly improved.

In terms of safety, there was no serious drug-related adverse reaction. The severity of most AE was mild to moderate (severity <3), all adverse events reported were common adverse events related to chemotherapy or disease situation in patients with lung cancer. During the study

period, no AE related to Shenqi Fuzheng Injection and DCVAC/Luca injection occurred. There were no adverse events in the analysis population of leukapheresis and within 24 hours after the beginning of leukapheresis. It shows that the safety of the new combination regimen is good, does not increase patient safety risks.

The results have shown the combination of TCM Shenqi Fuzheng injection therapy is superior to traditional therapy. The promising survival benefit and good tolerance may provide us a new treatment idea. But the benefit of survival remains to be further confirmed by large sample randomized controlled trials.

In recent years, the finding that PD-1 blockade produces clinical responses in NSCLC has yielded increased interest in cancer vaccines and their possible combination with checkpoint inhibitors.[36-39] We can hypothesize DC treatment combined with immune checkpoint inhibitors might enhance the anti-tumor effect, which deserves further more investigation.

Meanwhile, our research has some limitations. The number of participants was small and the outcome of individual differences may be affected by different chemotherapy and unknown types of rare gene mutations. Additionally, diversity of oral Chinese medicine schemes may cause minor differences. Also, tongue diagnosis and constitution TCM evaluation was conducted by the same physician before and after treatment which would result in bias. In further studies, the physician may conduct blind evaluations on TCM constitution and tongue diagnosis by utilizing modern instruments such as robots to ensure assessments are more objective. In consideration of so many confounding factors, we will include many more cases in further study and may conduct a combination therapy of DCVAC/LuCa with PD-1/PD-L1 inhibitors and SoC in specific patients who may benefit from immunotherapy in the first-line therapy.

Conclusion

DCVAC/LuCa, combined with standard of care chemotherapy and Shenqi Fuzheng injection exhibited good benefit in improving survival in Chinese patients with recurrent metastatic or advanced NSCLC, and showed good tolerance with no related adverse events. But this study is a single-arm phase II clinical trial, and a further randomized controlled phase III clinical investigation with a large population-based sample size is needed.

Acknowledgments

The authors thank all the patients who participated in this study. We thank the SOTIO a.s. and SOTIO Medical Research(Beijing) Co., Ltd. staffs who supported this study, including Fan Zhang, Yong Zhang, Shuangyan Gao, Shumin Wang, Qian Ge. We thank the nurses from Department of Integrative Oncology, China-Japan Friendship Hospital, including Wenli Lang, Hongying Qi, Liangliang Li, Kun Wang, Fang Liu, Yongxia Zhao, and Xinying Zhang for their nursing work in DCVAC/LuCa therapy.

Author Contributions

Qing Liu and Yanni Lou are co–first authors. Liqun Jia proposed the concept of the study. Qing Liu and Yanni Lou were the drafters of the manuscript. Yanni Lou, Qing Liu, Liya Li, Guowang Yang, Zhiqiang Cheng, Huijuan Cui, Yuan Li, Meng Liu, Yongxia Yan, Chao Deng, and Donggui Wan contributed to the screening, treatment, and follow-up of patients enrolled. All authors participated in the design of the study and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Scientific Research Project of China-Japan Friendship Hospital (2015-HX-21).

ORCID iDs

Qing Liu https://orcid.org/0000-0001-8534-3384
Yanni Lou https://orcid.org/0000-0003-3181-494X

References

1. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006;24:4539-4544. doi:10.1200/JCO.2005.04.4859
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424. doi:10.3322/caac.21492
3. Cao M, Chen W. Epidemiology of lung cancer in China. *Thorac Cancer*. 2019;10:3-7. doi:10.1111/1759-7714.12916
4. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39-51. doi:10.1016/j.jtho.2015.09.009
5. Cardenal F, López-Cabrerizo MP, Antón A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 1999;17:12-18. doi:10.1200/JCO.1999.17.1.12
6. Kelly K, Crowley J, Bunn PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol*. 2001;19:3210-3218. doi:10.1200/JCO.2001.19.13.3210

7. Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. *J Thorac Oncol*. 2015;10:134-142. doi:10.1097/JTO.0000000000000366
8. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543-3551. doi:10.1200/JCO.2007.15.0375
9. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31:2895-2902. doi:10.1200/JCO.2012.47.1102
10. Malhotra J, Jabbour SK, Aisner J. Current state of immunotherapy for non-small cell lung cancer. *Transl Lung Cancer Res*. 2017;6:196-211. doi:10.21037/tlcr.2017.03.01
11. Podrazil M, Horvath R, Becht E, et al. Phase I/II clinical trial of dendritic-cell based immunotherapy (DCVAC/PCa) combined with chemotherapy in patients with metastatic, castration-resistant prostate cancer. *Oncotarget*. 2015;6:18192-18205. doi:10.18632/oncotarget.4145
12. Naylor EC, Desani JK, Chung PK. Targeted therapy and immunotherapy for lung cancer. *Surg Oncol Clin N Am*. 2016;25:601-609. doi:10.1016/j.soc.2016.02.011
13. Qi F, Zhao L, Zhou A, et al. The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer. *Biosci Trends*. 2015;9:16-34. doi:10.5582/bst.2015.01019
14. Dong J, Su SY, Wang MY, Zhan Z. Shenqi fuzheng, an injection concocted from Chinese medicinal herbs, combined with platinum-based chemotherapy for advanced non-small cell lung cancer: a systematic review. *J Exp Clin Cancer Res*. 2010;29:137. doi:10.1186/1756-9966-29-137
15. Yang Y, Ting W, Xiao L, et al. Immunoregulation of Shenqi Fuzheng injection combined with chemotherapy in cancer patients: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2017;2017:512-538.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247. doi:10.1016/j.ejca.2008.10.026
17. National Cancer Institute. Common terminology criteria for adverse events v4.03. Accessed June 14, 2010. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
18. Beltran H, Beer TM, Carducci MA, et al. New therapies for castration-resistant prostate cancer: efficacy and safety. *Eur Urol*. 2011;60:279-290. doi:10.1016/j.eururo.2011.04.038
19. Simpson GR, Relph K, Harrington K, Melcher A, Pandha H. Cancer immunotherapy via combining oncolytic virotherapy with chemotherapy: recent advances. *Oncolytic Virother*. 2016;5:1-13. doi:10.2147/OV.S66083
20. Chajon E, Castelli J, Marsiglia H, De Crevoisier R. The synergistic effect of radiotherapy and immunotherapy: a promising but not simple partnership. *Crit Rev Oncol Hematol*. 2017;111:124-232. doi:10.1016/j.critrevonc.2017.01.017
21. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. *Nat Rev Cancer*. 2012;12:265-277. doi:10.1038/nrc3258
22. Lövgren T, Wolodarski M, Edbäck U, et al. Abstract CT032: adoptive T cell transfer combined with DC vaccination in patients with metastatic melanoma. *Cancer Res*. 2018;78:CT032. doi:10.1158/1538-7445
23. Fucikova J, Moserova I, Truxova I, et al. High hydrostatic pressure induces immunogenic cell death in human tumor cells. *Int J Cancer*. 2014;135:1165-1177. doi:10.1002/ijc.28766
24. Zemanova M, Cernovska M, Havel L, et al. Autologous dendritic cell-based immunotherapy (DCVAC/LuCa) and carboplatin/paclitaxel in advanced non-small cell lung cancer: a randomized, open-label, phase I/II trial. *Cancer Treat Res Commun*. 2021;28:100427. doi:10.1016/j.ctarc.2021.100427
25. Wang L, Qu H. Development and optimization of SPE-HPLC-UV/ELSD for simultaneous determination of nine bioactive components in Shenqi Fuzheng injection based on quality by design principles. *Anal Bioanal Chem*. 2016;408:2133-2145.
26. Ai Q, Zhang W, Xie Y, Huang W, Liang H, Cao H. Post-marketing safety monitoring of Shenqifuzheng injection: a solution made of Dangshen (Codonopsisnopsis) and Huangqi (Radix Astragali Mongolici). *J Tradit Chin Med*. 2014;34:498-503.
27. Li W, Xu Q, He YF, et al. Anti-tumor effect of steamed Codonopsis lanceolata in H22 tumor-bearing mice and its possible mechanism. *Nutrients*. 2015;7:8294-8307.
28. Dong BY, Wang C, Tan L, et al. Inhibitory effect of Shenqi Fuzheng injection combined with docetaxel on lung cancer cells. *J Zhejiang Univ Sci B*. 2017;18:76-78.
29. Xiong Y, Zhao Q, Gu L, Liu C, Wang C. Shenqi Fuzheng injection reverses cisplatin resistance through mitofusin-2-mediated cell cycle arrest and apoptosis in A549/DDP cells. *Evid Based Complement Alternat Med*. 2018;2018:8258246.
30. Du J, Cheng BC, Fu XQ, et al. In vitro assays suggest Shenqi Fuzheng injection has the potential to alter melanoma immune microenvironment. *J Ethnopharmacol*. 2016;194:15-19.
31. Wu JZ, Jin JX, Liu LT. Shenqifuzheng injection combined pemetrexed sodium and cisplatin in the treatment of advanced non-small cell lung cancer. *Oncol Prog*. 2021;19:1341-1344. doi:10.11877/j.issn.1672-1535.2021.19.13.12
32. Lin HS, Li DR. [Multi-center randomized clinical study on Shenqi-fuzheng injection combined with chemotherapy in the treatment for lung cancer]. *Zhonghua Zhong Liu Za Zhi*. 2007;29:931-934. doi:10.3760/j.issn:0253-3766.2007.12.012
33. Wen GH, Jian LY, Yang GD, et al. Effect of Shenqi Fuzheng injection on palliative treatment of advanced qi deficiency in non-small cell lung cancer. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2019;19:151-152. doi:10.13638/j.issn.1671-4040.2019.03.075

34. Mitchell DA, Batich KA, Gunn MD, et al. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients. *Nature*. 2015;519:366-369. doi:10.1038/nature14320
35. China Association of Chinese Medicine. *Classification and Determination of Constitution in TCM*. 1st ed. China Traditional Chinese Medicine Press; 2009.
36. Langer CJ. Emerging immunotherapies in the treatment of non-small cell lung cancer (NSCLC): the role of immune checkpoint inhibitors. *Am J Clin Oncol*. 2015;38:422-430. doi:10.1097/COC.0000000000000059
37. Davar D, Kirkwood JM. PD-1 immune checkpoint inhibitors and immune-related adverse events: understanding the upside of the downside of checkpoint blockade. *JAMA Oncol*. 2019;5:942-943. doi:10.1001/jamaoncol.2019.0413
38. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092. doi:10.1056/NEJMoa1801005
39. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051. doi:10.1056/NEJMoa1810865