Hydrogen therapy can be used to control tumor progression and alleviate the adverse events of medications in patients with advanced non-small cell lung cancer

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Abstract

Chemotherapy, targeted therapy, and immunotherapy are used against advanced non-small cell lung cancer. A clinically efficacious method for relieving the adverse events associated with such therapies is lacking. Fifty-eight adult patients were enrolled in our trial to relieve pulmonary symptoms or the adverse events of drugs. Twenty patients who refused drug treatment were assigned equally and randomly to a hydrogen (H2)-only group and a control group. According to the results of tumor-gene mutations and drug-sensitivity tests, 10, 18, and 10 patients were enrolled into chemotherapy, targeted therapy, and immunotherapy groups in which these therapies were combined with H2-therapy, respectively. Patients underwent H2 inhalation for 4–5 hours per day for 5 months or stopped when cancer recurrence. Before study initiation, the demographics (except for tumor-mutation genes) and pulmonary symptoms (except for moderate cough) of the five groups showed no significant difference. During the first 5 months of treatment, the prevalence of symptoms of the control group increased gradually, whereas that of the four treatment groups decreased gradually. After 16 months of follow-up, progression-free survival of the control group was lower than that of the H2-only group, and significantly lower than that of H2+ chemotherapy, H2+ targeted therapy, and H2+ immunotherapy groups. In the combined-therapy groups, most drug-associated adverse events decreased gradually or even disappeared. H2 inhalation was first discovered in the clinic that can be used to control tumor progression and alleviate the adverse events of medications for patients with advanced non-small cell lung cancer. This study was approved by the Ethics Committee of Fuda Cancer Hospital of Jinan University on December 7, 2018 (approval No. Fuda20181207), and was registered at ClinicalTrials.gov (Identifier: NCT03818347) on January 28, 2019.

Key words: adverse event; chemotherapy; hydrogen; immunotherapy; non-small-cell lung cancer; NSCLC; PFS; progression-free survival; targeted drug

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INTRODUCTION

Lung cancer is the most prevalent form of cancer-related disease worldwide, of which non-small-cell lung cancer (NSCLC) accounts for ~83%. Many patients are at an advanced stage of lung cancer when the diagnosis is made, and progression-free survival (PFS) is usually < 6 months. In these cases, the tumors cannot be resected; therefore, chemotherapy, targeted therapy, and immunotherapy are common treatment options. Each treatment has different indications, and also produces different adverse events. Serious adverse events (e.g., severe granulocytopenia, thrombocytopenia, abnormal liver function) often lead to significant changes in vital signs and patients are forced to stop or change medications.

Hydrogen (H2) is an anti-inflammatory, antioxidant, and antiapoptotic molecule. It can diffuse into mitochondria, neutralize reactive oxygen species selectively, and restore cell viability by regulating expression of various genes. In animal experiments, H2 has been demonstrated to alleviate the serious adverse events caused by chemotherapy, and targeted therapy. H2 has been used in clinical trials of multiple non-neoplastic diseases, indicating the safety of H2 gas inhalation.

In the present study, H2 therapy was used to control cancer progression and alleviate the adverse events of multiple standard therapies in patients with advanced NSCLC.

SUBJECTS AND METHODS

The inclusion and exclusion criteria

This clinical trial was registered at ClinicalTrials.gov (Identifier: NCT03818347) on January 28, 2019. The enrolled patients were divided into five groups according to the precise medical test results of tumors. The inclusion criteria were patients with: stage-III or -IV NSCLC diagnosed by imaging and pathology with specialist doctor; tumor number 1–6; maximum tumor length < 2 cm; Karnofsky performance status (KPS) score ≥ 70; expected survival time > 6 months; platelet count ≥ 80 × 109/L; white blood cell count ≥ 3 × 109/L; neutrophil count ≥ 2 × 109/L; hemoglobin ≥ 80 g/L. The exclusion criteria were patients with: a cardiac pacemaker; brain metastasis; grade-3 hypertension or diabetic complications; severe cardiac and pulmonary dysfunction. This study protocol received ethical approval from the Ethics Committee of Fuda Cancer Hospi-
tal of Jinan University on December 7, 2018 (approval No. Fuda20181207). Written informed consent was obtained from each patient.

**Subjects**
Between June and September 2019, 58 patients with advanced NSCLC at Fuda Cancer Hospital of Jinan University met the inclusion criteria mentioned above and were enrolled in the study. Thirty-four patients had surgery before enrollment, and 24 patients were in advance stage when diagnosis.

Immunohistochemical assays of the ratio of programmed cell death-1: programmed cell death-1 ligands, tumor mutation burden, and microsatellite instability in tumor specimens were undertaken. Based on the results, 10 patients were administered a drug based on antibodies against programmed cell death-1 (Nivolumab [Opdivo®, Bristol-Myers Squibb, New York, NY, USA] or Pembrolizumab [Keytruda®, Merck, Kennyworth, NJ, USA]). Through detection of gene mutations in tumor specimens, 18 patients were selected to be given targeted therapy. Patients with a mutation in the epidermal growth factor receptor gene were administered Osimertinib (Tagrisso®, AstraZeneca, London, UK), Gefitinib (Iressa®, AstraZeneca) or Erlotinib (Tarceva®, Roche, Basel, Switzerland). Patients with a mutation in the anaplastic lymphoma kinase gene or receptor tyrosine kinase-1 gene were administered Crizotinib (Xalkori®, Pfizer, New York, NY, USA). Based on the data of drug-sensitivity tests, 10 patients were administered chemotherapy (Cisplatin or Carboplatin [both from Qilu Pharmaceuticals, Haikou, Hainan Province, China]).

The remaining 20 patients who were not sensitive to common drugs or who failed to respond to treatment by common drugs were distributed evenly in the H₂-monotherapy group or control group. Three groups of patients who had H₂ treatment combined with another treatment (immunotherapy, targeted therapy or chemotherapy) started therapy before enrollment of our clinical trial. Most of those patients experienced significant effects on cancer-related lung symptoms after taking combination therapy, but new drug-related adverse events emerged. Lung symptoms or drug-related adverse events were compared before and after H₂ treatment. The comparison of lung symptoms before hydrogen treatment and the changes of tumor or drug-related symptoms in each group after hydrogen treatment are shown in Figure 1. This study followed the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) Statement.

**H₂ inhalation**
H₂ was produced by a H₂-oxygen nebulizer (H₂, 66.7% and oxygen 33.3%; maximum gas flow, 3 L/min; AMS-H-03, Shanghai Asclepius Meditec, Shanghai, China). The control group underwent a sham procedure (H₂, 0% and oxygen 33.3%; maximum gas flow, 3 L/min; Shanghai Asclepius Meditec). Enrolled patients inhaled the gas mixture for 4–6 hours every day and underwent imaging examination every month until the existing lesions progressed significantly or new metastases appeared. PFS was calculated from the start of H₂ inhalation to tumor progression. All patients received computed tomography or magnetic resonance examination every month. If the existing tumors grew up significantly or new metastases appeared, it is considered as tumor progression.

**Pulmonary symptoms and drug-associated adverse events**
The respiratory function of enrolled patients before H₂ therapy was assessed by very experienced respiratory physicians using a pulmonary function tester (Autospiro AS-507; Minato Medical Science, Tokyo, Japan). Pulmonary tumor-related symptoms and the KPS score of all patients before H₂ inhalation were evaluated. The adverse events of chemotherapy, targeted therapy or immunotherapy were assessed by the same respiratory physicians according to Common Terminology Criteria for Adverse Events 5.0.

**Statistical analyses**
Before H₂ treatment, the demographics and tumor-associated symptoms of patients were compared using chi-squared and Fisher’s exact tests; respiratory function and the KPS score were compared using one-way analysis of variance and Bonferroni’s multiple comparison test. After H₂ treatment, each tumor-associated symptom and drug-associated adverse event was compared using linear regression analysis; the PFS of each group was compared by one-way analysis of variance and Bonferroni’s multiple comparison test. P < 0.05 was considered significant difference. Analyses were done using Prism 5.0 (GraphPad, San Diego, CA, USA).

**RESULTS**
**Clinical data of advanced non-small cell lung cancer patients with H₂ inhalation treatment**
Patients underwent H₂ inhalation per day for 5 months or stopped the inhalation when cancer relapsed. There was no significant difference in most patient characteristics (e.g., sex) in each group. However, the targeted therapy–H₂-therapy group had a higher proportion of tumor-gene mutations than...
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Pulmonary signs and symptoms of advanced non-small cell lung cancer patients with H₂ inhalation treatment

Before the start of H₂ therapy, there was no significant difference in pulmonary function or the KPS score among the five groups of patients (Table 2). The prevalence of most pulmonary symptoms (e.g., mild dyspnea, non-cardiac chest pain, pleural effusion, and hemoptyis) was similar among groups. The prevalence of most pulmonary symptoms in the control group, H₂-monotherapy group, and immunotherapy–H₂-therapy group was higher than that in the target therapy–H₂-therapy group and chemotherapy–H₂-therapy group (P = 0.0137).

Tumor-associated symptoms of advanced non-small cell lung cancer patients with H₂ inhalation treatment

At the beginning of H₂ treatment, the prevalence of tumor-associated symptoms in the control group and H₂-monotherapy group was similar (P = 0.9994). With prolongation of the treatment time, in the control group, the prevalence of moderate cough (P = 0.0023), mild dyspnea (P = 0.0019), mild non-cardiac chest pain (P = 0.0006), mild pleural effusion (P = 0.0023), and mild hemoptyis (P = 0.0028) increased significantly (Figure 2A). In the H₂-monotherapy group, the prevalence of moderate cough (P = 0.0014), mild dyspnea (P = 0.0247), mild non-cardiac chest pain (P = 0.0136), mild pleural effusion (P = 0.0015), and mild hemoptyis (P = 0.0048) increased significantly compared to the other four groups (P = 0.005; Table 1).

Table 1: Patient demographics of advanced non-small cell lung cancer patients in different groups

|                  | Control (n = 10) | H₂ (n = 10) | Immuno-H₂ (n = 10) | Target-H₂ (n = 18) | Chemo-H₂ (n = 10) | P-value |
|------------------|-----------------|-------------|-------------------|--------------------|------------------|---------|
| Sex              |                 |             |                   |                    |                  |         |
| Female           | 7 (70)          | 5 (50)      | 4 (40)            | 12 (67)            | 6 (60)           | 0.5991  |
| Male             | 3 (30)          | 5 (50)      | 6 (60)            | 6 (33)             | 4 (40)           |         |
| Age (yr)         |                 |             |                   |                    |                  |         |
| 41–60            | 4 (40)          | 4 (40)      | 7 (70)            | 8 (44)             | 6 (60)           | 0.6239  |
| 61–70            | 3 (30)          | 5 (50)      | 3 (30)            | 6 (33)             | 3 (30)           |         |
| 71–80            | 3 (30)          | 1 (10)      | 0                 | 4 (22)             | 1 (10)           |         |
| Pathology        |                 |             |                   |                    |                  | 0.9999  |
| Adenocarcinoma   | 6 (60)          | 7 (70)      | 7 (70)            | 12 (67)            | 7 (70)           |         |
| Squamous cell carcinoma | 3 (30) | 2 (20) | 2 (20) | 4 (22) | 2 (20) |         |
| Large cell cancer| 1 (10)          | 1 (10)      | 1 (10)            | 2 (11)             | 1 (10)           |         |
| TNM stage        |                 |             |                   |                    |                  | 0.21    |
| III              | 2 (20)          | 0           | 0                 | 3 (17)             | 3 (30)           |         |
| IV               | 8 (80)          | 10 (100)    | 10 (100)          | 15 (83)            | 7 (70)           |         |
| Tumor number     | 15              | 12          | 15                | 32                 | 12               | 0.6716  |
| Lung, mediastinum and pleura | 6 (40) | 5 (42) | 5 (33) | 12 (38) | 6 (50) |         |
| Brain            | 3 (20)          | 1 (8)       | 1 (7)             | 7 (22)             | 4 (33)           |         |
| Bone             | 4 (27)          | 5 (42)      | 5 (33)            | 9 (28)             | 2 (17)           |         |
| Others           | 2 (13)          | 1 (8)       | 4 (27)            | 4 (12)             | 0               |         |
| Tumor-gene mutation | 3 (30) | 1 (10) | 2 (20) | 14 (78) | 5 (50) |         |
| EGFR             | 1 (10)          | 2 (20)      | 0                 | 3 (17)             | 0               |         |
| ALK              | 1 (10)          | 0           | 0                 | 1 (5)              | 0               |         |
| Not found        | 5 (50)          | 7 (70)      | 8 (80)            | 0                  | 5 (50)           |         |

Note: Data are expressed as number (percent), and analyzed by chi-squared and Fisher’s exact tests. H₂: Hydrogen; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ROS: receptor tyrosine kinase; TNM: tumor-node-metastasis.

Figure 2: Tumor-associated symptoms varied with the inhalation time of hydrogen (H₂).

Note: (A) Control group (inhalation of 33.3% oxygen gas and no H₂ (n = 10). (B) H₂ only group (inhalation of 66.7% H₂ + 33.3% O₂) (n = 10). Each tumor-associated symptom was compared using linear regression analysis.
Drug-associated adverse events of advanced non-small cell lung cancer patients with H₂ inhalation treatment

At the beginning of H₂ treatment, the prevalence of tumor-associated symptoms in the three groups was similar (P = 0.5120), but drug-associated symptoms in the three groups were quite different (Figure 3). With the prolongation of treatment time, the prevalence of cough and non-cardiac chest pain (P = 0.0013), maculopapular rash (P = 0.0021), hepatobiliary disease (P = 0.0064), and dizziness and headache (P = 0.0111) decreased significantly, but diarrhea did not (P = 0.4144) (Figure 3A). In the target therapy–H₂-therapy group, the prevalence febrile granulocytopenia (P = 0.0026), nausea and vomiting (P = 0.0051), maculopapular rash (P < 0.0001), insomnia (P = 0.0144), and oral mucositis (P = 0.0007) decreased significantly (Figure 3B). In the chemotherapy–H₂-therapy group, the prevalence of febrile granulocytopenia (P = 0.0086), anemia and thrombocytopenia (P = 0.0009), constipation and diarrhea (P = 0.0053) and anorexia (P = 0.0129) decreased significantly, but nausea and vomiting did not (P = 0.0720; Figure 3C).

PFs of advanced non-small cell lung cancer patients with H₂ inhalation treatment

After 16 months of follow-up, all 58 patients developed tumor progression. PFS for the control group was 4.4 ± 1.2 months, whereas that for the H₂-only group was 7.9 ± 2.2 months, H₂-immunotherapy group was 10.1 ± 2.6 months, H₂-targeted therapy group was 9.4 ± 3.1 months, and H₂-chemotherapy group was 8.5 ± 3.0 months. PFS of the four treatment groups was longer than that of the control group, and that of the three H₂ therapy-combination groups was prolonged significantly (Figure 4).

Discussion

Molecular H₂ has been used to treat pulmonary symptoms in animal models of acute lung injury,¹⁸–¹⁻¹ asthma²² and chronic obstructive pulmonary disease.²³⁻²⁵ The principle of H₂ therapy includes inhibition of secretion of cytokines such as interleukin-4, interleukin-13, interleukin-6 and tumor necrosis factor-α.¹⁵ H₂ therapy can alleviate pulmonary inflammation without impairing anti-tumor effects.²⁶⁻²⁸ Therefore, H₂ gas can

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Table 2: Pulmonary signs and symptoms before hydrogen therapy of advanced non-small cell lung cancer patients with H₂ inhalation treatment

|                  | Control (n = 10) | H₂ only (n = 10) | Immuno-H₂ (n = 10) | Target-H₂ (n = 18) | Chemo-H₂ (n = 10) | P-value |
|------------------|-----------------|-----------------|-------------------|--------------------|-----------------|---------|
| **Respiratory function** |                 |                 |                   |                    |                 |         |
| FEV1 (L)         | 1.57±0.59       | 1.63±0.52       | 1.54±0.59         | 1.56±0.49          | 1.56±0.52       | 0.3897  |
| FVC (L)          | 1.82±0.57       | 1.93±0.47       | 1.75±0.33         | 1.83±0.56          | 1.91±0.35       | 0.4623  |
| KPS score        | 76±7            | 78±8            | 76±7              | 77±7               | 78±8            | 0.4007  |
| **Tumor-associated symptoms** |               |                 |                   |                    |                 |         |
| Moderate cough   | 6               | 7               | 5                 | 2                  | 3               | 0.0137  |
| Mild dyspnea     | 5               | 5               | 2                 | 3                  | 2               | 0.0757  |
| Non-cardiac chest pain | 4           | 4               | 2                 | 4                  | 2               | 0.6666  |
| Mild pleural effusion | 3           | 3               | 1                 | 3                  | 2               | 0.748   |
| Mild hemoptysis  | 2               | 2               | 0                 | 3                  | 0               | 0.3683  |

Note: Data are expressed as mean ± SD or number. Respiratory function and the KPS score were compared using one-way analysis of variance and Bonferroni’s multiple comparison tests. Tumor-associated symptoms were compared using chi-squared and Fisher’s exact tests. H₂: hydrogen; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; KPS: Karnofsky performance status.
be adopted as adjuvant therapy to suppress these symptoms.

Chemotherapy, targeted therapy, and immunotherapy are first-line treatments against advanced NSCLC. The vastly increased generation of reactive oxygen species during treatment is believed to contribute to adverse events, resulting in oxidative stress, inflammation and apoptosis. In the present study, H₂ therapy was shown to alleviate drug-related adverse events, most of which have been reported in animal models, including lung injury caused by various factors, hepatobiliary diseases, maculopapular rash, diarrhea and constipation, nausea and vomiting, oral mucositis, anemia, thrombocytopenia, and anorexia. We found that the prevalence of insomnia, dizziness and headache could be reduced significantly after H₂ inhalation, which could be related to relief of diseases of the central nervous system, such as cerebral hemorrhage, Parkinson’s disease and Alzheimer’s disease, observed in animal experiments. The mechanism of action observed in animal experiments could be used as a reference for clinical research. Surprisingly, H₂ therapy, which is non-toxic and can alleviate adverse events in multiple organs simultaneously, has been used rarely.

We found that H₂ monotherapy could prolong the PFS of patients with advanced NSCLC from 4.4 ± 1.2 months to 7.9 ± 2.2 months, suggesting that H₂ could inhibit the growth of lung cancer cells independently. This hypothesis has been bolstered by data from an in vitro and in vivo study, which confirmed that H₂ can inhibit the proliferation, migration, and invasion of the lung-cancer cell lines and tumor growth in mouse model. These data suggested that H₂ could serve as new therapy against lung cancer. However, for patients eligible for first-line treatment, drugs will produce more pronounced effects upon tumor control. Whether a combination of drug therapy and H₂ therapy can elicit better tumor control must be studied further, but gradual reduction of most drug-associated adverse events after H₂ inhalation is clear.

Several delivery methods of molecular H₂ are available and convenient: inhalation, drinking H₂-saturated water, injection with H₂-saturated saline, and taking a “H₂ bath.” H₂ is non-toxic, inexpensive, can be administered readily, can diffuse into tissues and cells and cross the blood–brain barrier. Hence, H₂ could be used to treat tumors of the head, neck and chest. Because of the risk of explosion of H₂ and oxygen mixed in air, often such gas mixtures are inhaled using catheters and masks whereas, in animal experiments, drinking or injection of H₂-dissolved water is employed. Use of a machine with a sufficiently high flow rate (3 L/min) and inhalation duration every day (4–6 hours) of H₂ in this trial may enable control of tumor growth and reduce the prevalence of adverse events of drugs.

In general, H₂ inhalation was first discovered in the clinic that can be used to control tumor progression and alleviate the adverse events of medications in patients with advanced NSCLC. The main limitation of this study is that the number of patients enrolled is relatively small, and more accurate patient benefits are still awaiting the results of large samples. Whether this therapeutic effect can be improved further, as well as determination of the synergistic effect of drugs and H₂ therapy, must be explored further.

Figure 4: Comparison of progression-free survival (PFS) between groups after hydrogen (H₂) treatment.

Note: PFS of each group was compared by one-way analysis of variance and Bonferroni’s multiple comparison test. *P < 0.05, **P < 0.01, ***P < 0.001.
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