A narrative review of hydrogen oncology: from real world survey to real world evidence

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Abstract

The use of hydrogen for cancer control has made great progress in cytology and animal experiments. With the increasing number of hydrogen products on the market, larger numbers of advanced cancer patients have participated in clinical trials or received treatment at home after purchase. Our study reported a real-world survey from 82 patients with good cancer control using hydrogen products, including real world evidence from patients who received ineffective traditional treatment, patients who received traditional treatment that failed, or patients who refused traditional treatment. Two typical cases were reported herein. Subsequently, we included studies on the mechanism of hydrogen oncology. The mechanism of cancer control using hydrogen includes the inhibition of tumor cells and the activation of exhausted lymphocytes. Large-scale real world evidence has shown clinical value, and yet remains to be further developed and researched.

Key words: cancer; hydrogen; lymphocyte; mechanism; real world evidence; real world survey; RWE; RWS

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Introduction

Hydrogen gas or molecular hydrogen has been confirmed as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals.[1] A TV program called "The Truth of Holy Water" was shown on the Discovery Truth channel in Japan on June 13, 1998. In summary, there is an abandoned mine pit in Nordennau, a well-known small town located in the northwestern part of Düsseldorf, Germany. Every year, thousands of people with a variety of diseases, including cancer, come to Nordennau aiming to find "holy water" from the local mine diggings to cure their illnesses. In April 1986, a group of children who suffered from leukemia resulting from the Chernobyl nuclear disaster were brought by the owner (Theo Tom) of the mine to drink the holy water. A few months later, most of the children presented with significant symptomatic improvement, among them one case showed complete recovery. These results caused a mass uproar in the media. Subsequently, it was discovered that the patient's improvements and recovery were due to the large amount of hydrogen gas contained in the holy water. Since a real world survey of 82 patients with advanced cancer from China was reported,[2] "hydrogen oncology" obtained the real world evidence for the first time. The articles used in this oncology review were retrieved by replicating the search terms of Chen et al.[2] An electronic search of the Medline database for literature describing clinical hydrogen therapy for cancer patients from 2000 to 2019. The results were further screened by title and abstract to only cancer treatment, not Complications treatment. The main cited article is from the latest Science Citation Index paper report in 2019.

Real World Survey of Hydrogen Oncology

Approximately 40 years ago, Dole et al.[3] reported that hydrogen exhibited effects on inhibiting squamous cell carcinoma cells. However, despite being published in the journal Science, the report did not attract much attention, possibly because hydrogen is simple and ordinary.

We have conducted a voluntary field survey in patients diagnosed with cancer who inhaled hydrogen at home or at rehabilitation centers from 2014 to 2019.[2] Follow-up was performed on 82 patients with advanced (stage III and IV) cancer. The patients used the Hydrogen-oxygen Atomizer (AMS-H-03, Shanghai Asclepius Meditec Co., Ltd., Shanghai, China), which provided 66.7% hydrogen with mixed 33.3% oxygen with gas flow at 3000 mL/min.

Real World Evidence of Hydrogen Oncology

Primary results of clinical observation

Follow-up time was between 3–46 months, with a median of 6 months. During the follow-up period, 12 patients died of disease progression and complications with stage IV cancer. The patient quality of life was prospectively evaluated by quality of life questionnaire core 30 (QLQ-C30).[4] All quality of life areas improved after four weeks of hydrogen inhalation, with the most significant improvements in fatigue, insomnia, loss of appetite, and pain. A performance status assessment was completed on all patients according to Zubrod-ECOG-WHO (ZPS, 5-point method),[5] and 41.5% of patients showed improved performance status, 34.1% of patients were stable, and 24.4% of patients declined. Lung cancer patients had the highest improvement rate, and pancreatic cancer and gynecologic cancer patients had the lowest improvement rate. Tumor markers, including alpha-fetoprotein, carcinoembryonic antigen, CA19-9, CA125, CA153, and CA724, were observed. A total of 58 cases exhibited one or more abnormal tumor markers. A

decrease of tumor markers was observed in 36.2% of patients, 15.5% of patients had stable expression of tumor markers, and 48.3% of patients showed a decline in tumor markers after 13–45 days (median 23 days) following hydrogen inhalation. The highest rate of tumor marker decrease was seen in lung cancer and the lowest in pancreatic and hepatic malignancies. A total of 80 cases had tumors that could be evaluated by image analysis. Evaluation of oncologic response according to the Response Evaluation Criteria in Solid Tumors criteria showed complete response in 1 case (1.3%), partial response in 15 cases (18.8%), stable disease in 30 cases (37.5%), and progressive disease in 34 cases (42.5%) after hydrogen inhalation, with a total disease control rate of 57.5%. Complete response and partial response appeared between 21–80 days with a median time of 55 days after hydrogen inhalation. The disease control rate was 83.0% and 47.7% in stage III and IV patients ($P < 0.05$), respectively. No hematological toxicity was observed. Stomach upset, dizziness, headache, and nasal mucus at the beginning of hydrogen inhalation were observed in individual cases but quickly disappeared spontaneously.[2]

Typical clinical cases

The hydrogen control of cancer confirmed by the real world survey is clearly illustrated in the following two cases.

Case 1

A 72-year-old female patient was hospitalized on September 20, 2018 with stage IV gallbladder cancer with massive intrahepatic and the lymph node metastases in the hilar area and around the head of the pancreas. There was involvement of the duodenum that caused upper gastrointestinal obstruction. Biopsy showed poorly differentiated adenocarcinoma. The patient was extremely exhausted, accompanied by severe anemia with hemoglobin as low as 37 g/L and severe hypoalbuminemia with albumin as low as 23 g/L. The patient had a history of rheumatic heart disease with recent cardiac failure, and fasting blood glucose had been elevated (up to 22 mM) for a long time. Blood tumor markers CA19-9, alpha-fetoprotein, and carcinoembryonic antigen were increased. In addition to receiving symptomatic and supportive care, any conventional "anti-cancer" treatment could not be used. Beginning on October 23, 2018 the patient volunteered to inhale hydrogen-oxygen mixed gas only through a nasal cannula, two hours per day initially, and gradually increased to 6 hours per day. After one month of hydrogen inhalation, the patient showed obvious pseudo-progression of the disease and quickly relieved after symptomatic treatments.[6] After 2 months of hydrogen inhalation, the patient's performance status showed significant improvement (decreased from 5 to 3). After 3 months of hydrogen inhalation, tumor markers were reduced to the normal reference range, and CT showed more than a 50% reduction in gallbladder tumors and multiple intrahepatic and hilar metastases (defined as partial response). The patient's blood sugar dropped to normal when insulin was no longer used. The patient was discharged on February 1, 2019. Currently, the patient continues to inhale hydrogen every day at home and is in the process of further improvement (recent performance status of 0).[7]

Case 2

A 44-year-old woman diagnosed with lung cancer with multiple metastases in November 2015. Oral targeted drugs were initiated after removal of brain metastases, and most lesions remained stable for 28 months. In March 2018, intracranial multiple metastases, as well as hydrocephalus accumulation in the third ventricle and lateral ventricles, and metastases in bone, adrenal gland, liver were noted. Hydrogen-gas monotherapy was started to control the tumor a month later. After 4 months, the size of multiple brain tumors was reduced significantly, and the amount of hydrocephalus in the third ventricle and lateral ventricles reduced significantly. After 1 year, all brain tumors had disappeared, and there were no significant changes in metastases in the liver and lung. These data show that, after standard treatments had failed, hydrogen-gas monotherapy elicited significant effective control of tumors (especially those in the brain), and survival time was lengthened.[8]

Case 3

Three patients with nasopharyngeal carcinoma developed binaural secretory otitis media 0.5, 2, and 12 years after radiotherapy, respectively. The secretions subsided after conventional drug and drainage treatments, but hearing continued to deteriorate until severe loss was documented in both ears. After examination of the eardrum and tympanum, patients were enrolled in the first half of 2019. After 0.5, 1 and 2 months of continuous hydrogen–oxygen therapy, our first three patients reported different levels of improvement in binaural hearing. This is the first report to show that, after treatment for nasopharyngeal carcinoma, hearing loss can be alleviated using hydrogen–oxygen therapy.[9]

Mechanisms of Hydrogen Cancer Control

Hydrogen gas suppresses tumor formation and growth

Hydrogen cancer control has been supported by serial experimental studies in cancer cells and tumor models, which have demonstrated the inhibitory effects of hydrogen on cancer cell formation as well as proliferation, viability, cell cycle, migration, and invasion of kidney[10] and liver[11] cancer cells. Hydrogen treatment has been shown to decrease the expression of CD34, demonstrating its anti-angiogenesis effects in ovarian cancer.[12] A previous finding showed that molecular hydrogen could markedly inhibit the sphere-forming ability of ovarian cancer cells, cervical cancer cells, and glioma cells.[12] There is evidence to suggest that hydrogen inhibited lung cancer progression through the down-regulation structural maintenance of chromosomes protein 3, a regulator for chromosome condensation.[13,14] In human esophageal squamous cell carcinoma (KYSE-70) cells, hydrogen exerted its anticancer effects via inducing hydrogen peroxide accumulation, cell cycle arrest, and apoptosis induction mediated by mitochondrial apoptotic pathways.[15] In a rat orthotopic glioma model, hydrogen gas was shown to inhibit several markers involved in stemness, resulting in the suppression of sphere formation, cell migration, invasion, and colony formation of glioma cells.[16]

Hydrogen gas restores exhausted $CD8^+$ T cells

Hydrogen has been shown to modulate immune function.

A previous report showed that inhalation of hydrogen gas decreased the abundance of exhausted terminal programmed cell death protein 1 (PD-1)$^+$ CD8$^+$ T cells, increased active terminal PD-1- CD8$^+$ T cells, and restored exhausted CD8$^+$ T cells to improve progression free survival and overall survival in patients with stage IV colorectal cancer.[17] Hydrogen gas was recently reported to activate peroxisome proliferator-activated receptor γ coactivator-1α, inactivation of which induces mitochondrial dysfunction. Thus, increasing evidence has shown that hydrogen gas can directly inhibit the growth of certain cancer cells and can restore the vitality of exhausted cytotoxic T lymphocytes (**Figure 1**).

Hydrogen gas reverses adaptive and innate immune system senescence

Twenty advanced non-small cell lung cancer (NSCLC) patients were enrolled to evaluate the immunosenescence of peripheral blood lymphocyte subsets before and after 2 weeks of hydrogen inhalation. Before treatment, the abnormally higher indexes included exhausted cytotoxic T cells, senescent cytotoxic T cells, and killer Vδ1 cells. After two weeks of hydrogen therapy, the number of exhausted and senescent cytotoxic T cells decreased to within the normal range, and there was an increase in killer Vδ1 cells. The abnormally lower indexes included functional helper and cytotoxic T cells, Th1, total NKT cells, killer NK, and Vδ2 cells. All six cell subsets increased to within the normal range after treatment. The current data indicate that the immunosenescence of advanced NSCLC involves nearly all lymphocyte subsets, and 2 weeks of hydrogen treatment can significantly improve most of these indexes.[18]

Hydrogen gas controls tumor progression and alleviate the adverse events of medications

Fifty-eight adult patients were enrolled to relieve pulmonary symptoms (e.g., moderate cough, mild dyspnea, mild non-cardiac chest pain, mild pleural effusion and mild hemoptysis) or the adverse events of drugs (e.g., severe granulocytopenia, thrombocytopenia and abnormal liver function). During the first 5 months of treatment, the prevalence of pulmonary symptoms of the control group (oxygen inhalation) increased gradually, whereas that of the four treatment groups (hydrogen inhalation only and combination with chemotherapy, target therapy and immunotherapy) decreased gradually. After 16 months of follow-up, progression-free survival of the control group was significantly shorter than that of the four treatment groups. In the three combination-therapy groups, most drug-associated adverse events decreased gradually or even disappeared.[19]

Challenges and Questions

Hydrogen medicine is new and using hydrogen to control cancer is unconventional for most people, including professional medical staff. According to our real world survey, inhaling hydrogen can improve quality-of-life and control cancer progression in patients with advanced cancer, and could prolong life expectancy. Professor Zhao-You Tang, a highly respected Chinese oncologist from Hepatoma Institute of Fudan University (China), stated the following: "I was very dubious about the use of hydrogen in cancer control when the first patient case showed to me. But when I was shown nearly 50 cases successively, I became convinced."[20]

Cancer treatment remains a huge challenge. As a simple, cheap, and safe way to control cancer, hydrogen can be used as a complimentary option to conventional therapies for cancer. We plan to continue to perform real world survey and show real world evidence toward establishing "hydrogen oncology."

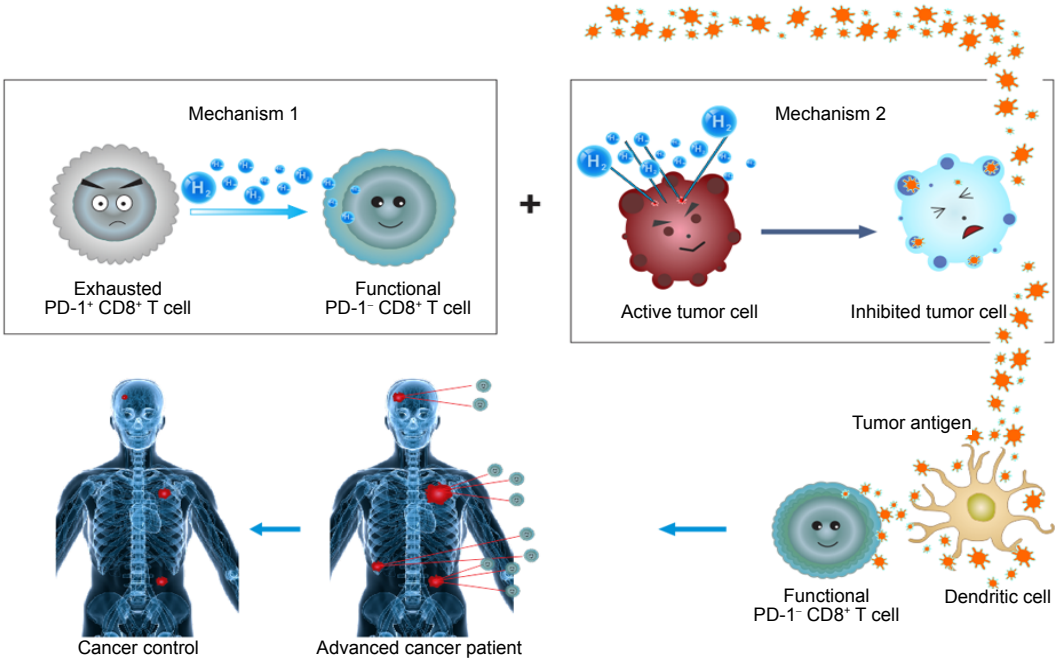

Figure 1: Two main mechanisms of hydrogen (H_2) cancer control.
Note: PD-1: Programmed cell death protein 1.

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Manuscript design: KCX and YYL; manuscript writing: KCX and JBC. All authors read and approved the final manuscript.
Conflicts of interest
The authors report no conflicts of interest in this work.
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