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A possible prevention strategy of radiation pneumonitis: Combine radiotherapy with aerosol inhalation of hydrogen-rich solution

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Radiotherapy is an important modality of cancer treatment. Radiation pneumonitis is a major obstacle to increasing the radiation dose in radiotherapy, and it is important to prevent this radiation-induced complication. Recent studies show that hydrogen has a potential as an effective and safe radioprotective agent by selectively reducing hydroxyl and peroxynitrite radicals. Since most of the ionizing radiation-induced cellular damage is caused by hydroxyl radicals, we hypothesize that a treatment combining radiotherapy with aerosol inhalation of a hydrogen-rich solution may be an effective and novel prevention strategy for radiation pneumonitis (hydrogen is explosive, while a hydrogen-rich solution such as physiological saline saturated with molecular hydrogen is safer).

key words: radiotherapy • pneumonitis • hydrogen • radioprotection

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BACKGROUND

Ionizing radiation is commonly used to treat many thoracic and chest wall malignancies, including primary carcinomas of the lung and breasts, Hodgkin's disease and metastases to the lung. Radiation pneumonitis can result in significant morbidity and mortality. This potentially life-threatening toxicity limits the dose of radiotherapy that can be administered to cancer patients and limits the possibility of curative treatment [1].

Recently, Ohsawa et al. [2] demonstrated that molecular hydrogen could selectively reduce cytotoxic reactive oxygen species, such as hydroxyl and peroxynitrite radicals, *in vitro* and exert therapeutic antioxidant activity in a rat middle cerebral artery occlusion model. Hydroxyl and peroxynitrite radicals are very strong oxidants that react indiscriminately with nucleic acids, lipids and proteins, resulting in DNA fragmentation, lipid peroxidation and protein inactivation. Yanfei et al. [3] found that hydrogen-rich saline could reduce lung injury induced by intestinal ischemia/reperfusion (I/R) in rats. Additionally, our department demonstrated that hydrogen treatment could protect cultured human lymphocyte AHH-1 cells and intestinal crypt HIEC cells from gamma radiation *in vitro*, and protect the gastrointestinal tract, the cardiovascular system from gamma radiation in mice [4–6]. Another possible mechanism underlying the cellular protection afforded by hydrogen may be an increase in antioxidant enzymes such as glutathione, superoxide dismutase or heme oxygenase-1 [7,8].

It has been considerably reported that free radical scavengers could effectively ameliorate the oxidative injuries due to IR [9]. Since reactive oxygen species (ROS) are the major mediators for radiation-induced damage, a treatment combining radiation with an antioxidant might provide a strategy for preventing radiation injury to normal tissues. The potential effect of a hydrogen-rich solution on radiation-induced pulmonary injury in which free radicals play an important role should not be ignored.

RADIATION PNEUMONITIS

Radiation pneumonitis is an inflammation of the lungs that can occur as an adverse effect of radiotherapy to the chest. The incidence varies widely among reports. Differences in radiation technique, method of reporting, and the evaluation of the symptoms themselves may account for this variability. The scoring of radiation pneumonitis is difficult, because coexisting medical conditions challenge the reliability of laboratory measurements [10]. With combined modality therapy with cytotoxic agents steadily being incorporated into clinical radiotherapy practice, a greater incidence of severe radiation pneumonitis is inevitable [11]. Without doubt, the incidence of radiation pneumopathy increases with concurrent drug administration. A recent study reported that taxane-based adjuvant chemotherapy, a standard regimen for high-risk breast cancer patients, increases the incidence of radiation pneumonitis to 35% [12].

The process of radiation pneumonitis is undoubtedly one of the most thought-provoking radiobiologic phenomena [10]. The early histopathologic finding is described as diffuse alveolar damage. This includes edema of the alveolar

walls, vessel thrombosis, intra-alveolar hemorrhage and infiltration with inflammatory cells [13]. Type I pneumocytes (covering 90% of the surface of the alveolar epithelium) are the first to be affected and to undergo apoptosis, leading to the accelerated proliferation of Type II epithelial cells (Type I precursors) and lung fibroblasts. Fibroblast proliferation and increased interstitial and intra-alveolar collagen accumulation are key pathogenetic features [10]. Quantitative and qualitative changes of the expression of genes after radiotherapy lead to the overproduction of a large number of cytokines and growth factors by irradiated cells, which act in an autocrine and paracrine fashion and give birth to the finally recognizable histopathologic changes and clinical syndromes [14,15]. Also, evidence from published data suggests that different cytokines initiate and sustain the inflammatory and fibrogenic processes associated with radiation pneumonitis [16–21]. TNF- α enhances phagocytosis and cytotoxicity in neutrophilic granulocytes and modulates the expression of other cytokines, including IL-1 and IL-6. TNF- α and IL-1 are strong chemoattractants for leukocytes, and they also increase their adherence to the endothelium by enhancing the expression of adhesion molecules [22]. IL-1 and IL-6 influence antigen-specific immune responses by induction of the differentiation of immature T cells into cytotoxic T cells and induction of the final maturation of B cells into immunoglobulin-secreting plasma cells and stimulation of the secretion of antibodies [23].

It was estimated that 60–70% of the ionizing radiation-induced cellular damage is caused by hydroxyl radicals [24]. Timely elimination of the hazard would presumably protect normal lung tissue from these damaging effects of radiotherapy to the chest on the root.

HYPOTHESIS

Our hypothesis is that a treatment combining radiotherapy with aerosol inhalation of a hydrogen-rich solution may be a safe, effective and novel prevention strategy for radiation pneumonitis. During radiotherapy to the chest, aerosol inhalation of a hydrogen-rich solution could quickly scavenge free radicals produced by irradiation in the normal lungs.

Based on recent experimental results, this theory has great significance. Firstly, molecular hydrogen can selectively reduce hydroxyl radicals and peroxynitrite *in vitro* and *in vivo* [2]. Hydrogen will react with only the strongest oxidants (hydroxyl radical and peroxynitrite) to produce water [25,26]. Hydrogen is mild enough not to disturb metabolic oxidation-reduction reactions or to disrupt ROS involved in cell signaling [27]. Secondly, hydrogen is an explosive gas, but if dissolved in a solution such as physiological saline or pure water, it will be safer (the saturation of hydrogen in the solution could reach 0.6 mmol/L) [4]. It is physiologically safe for patients to inhale a hydrogen-rich solution at a proper dose because hydrogen is continuously produced by colonic bacteria in the body and it normally circulates in blood [28]. Thirdly, hydrogen-rich saline attenuates lung injury induced by intestinal I/R. Free radicals are considered to be involved in the reoxygenated tissues and to be responsible for the development of acute respiratory distress syndrome in the pathological process of I/R injury [3,29–31]. Fourthly, it was demonstrated that hydrogen has radioprotective effects *in vitro* and *in vivo*. Treating cells with hydrogen

before irradiation could significantly inhibit ionizing radiation-induced cultured human cells apoptosis, and increase cells' viability *in vitro*. Hydrogen can also protect the gastrointestinal tract, the cardiovascular system from radiation-induced injury, decrease plasma malondialdehyde intestinal 8-hydroxydeoxyguanosine levels, and increase plasma endogenous antioxidants *in vivo* [4–6]. Because this strategy proposes a prophylactic use for hydrogen and goes beyond the current thinking that hydrogen can only be used as energy source, it is unprecedented.

EVALUATION

An ideal radioprotector should be able to specifically protect normal tissues from damage caused by irradiation, and should not weaken the effect of radiotherapy [32]. Hydrogen is a highly diffusible gas, and can penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus. Although hyperbaric hydrogen therapy could cause a marked regression of squamous cell carcinoma [33], hydrogen can enter and protect the tumor from radiotherapy. We hope that the effect of hydrogen will be limited to the normal lungs. Aerosol inhalation of a hydrogen-rich solution would be an ideal way to reach a relatively high concentration in the lungs and to produce local effects.

Water radiolysis occurs on a time scale of 10^{-18} – 10^{-12} seconds, and most of the radical reactions are completed within 1 second [34]. The free radicals developed through water radiolysis must be eliminated quickly and continuously. The 2 treatments (radiotherapy to the chest and aerosol inhalation of a hydrogen-rich solution) should be administered simultaneously.

CONCLUSIONS

Although modern techniques of radiotherapy (e.g., stereotactic radiotherapy, intraoperative radiotherapy, interstitial brachytherapy) and radioprotectors (e.g., thiol compounds, cytokines, immunomodulators, vitamin E, flavonoids) are now increasingly used to improve dose distribution and reduce adverse effects, radiation pneumonitis still occurs. There has been remarkably little progress in the development of effective therapies against radiation pneumonitis [35]. This hypothesis provides us with a new idea. With the progress of laboratory and clinical research, we believe that hydrogen-rich solution will give us more hope for the prevention of radiation pneumonitis.

Conflict of Interest

The author has no conflict of interest to disclose.

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