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

ARTICLE *in* MEDICAL SCIENCE MONITOR: INTERNATIONAL MEDICAL JOURNAL OF EXPERIMENTAL AND CLINICAL RESEARCH · APRIL 2011

Impact Factor: 1.43 · DOI: 10.12659/MSM.881698 · Source: PubMed

© Med Sci Monit, 2011; 17(4): HY1-4
PMID: 21455114

Received: 2010.10.25
Accepted: 2010.12.02
Published: 2011.04.01

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

Yunhai Chuai[AE]*, Luqian Zhao[A]*, Jin Ni[A]*, Ding Sun[B], Jianguo Cui[C], Bailong Li[D], Liren Qian[E], Fu Gao[F], Jianming Cai[FG]

* Authors contributed equally to this paper

Department of Radiation Medicine, Faculty of Naval Medicine, 2nd Military Medical University, Shanghai, PR China

Source of support: This work was supported by a grant from the National Natural Science Foundation of China (Grant No. 81072241)

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**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=881698
Word count: 1271
Tables: –
Figures: –
References: 35

Author's address: Jianming Cai and Fu Gao, Department of Radiation Medicine, Faculty of Naval Medicine, 2nd Military Medical University, Xiangyin Road, 200433, Shanghai, PR China, e-mail: cjm882003@yahoo.com.cn and gaofu_2002@yahoo.com.cn

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 caner 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.

References:

1. NM Woltman, Y Garces, K Olivier, R Miller: Incidence of radiation pneumonitis after thoracic intensity modulated radiation therapy. Int J Radiation Oncology Biol Phy, 2010; 78: S738
2. Ohsawa I, Ishikawa M, Takahashi K et al: Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med, 2007; 13: 688–94
3. Yanfei M, Xingfeng Z, Jianmei C: Hydrogen-rich saline reduces lung injury induced by intestinal ischemia/reperfusion in rats. Biochem Biophys Res Commum, 2009; 381: 602–5
4. Liren Q, Fei C, Jianguo C: Radioprotective effect of hydrogen in cultured cells and mice. Free Radic Res, 2010; 44: 275–82
5. Liren Q, Bailong L, Fei C et al: Hydrogen-rich PBS protects cultured human cells from ionizing radiation-induced cellular damage. Nuclear Technology & Radiation Protection, 2010; 25: 23–29
6. Liren Q, Fei C, Jianguo C: The potential cardioprotective effects of hydrogenin irradiated mice. J Radiat Res, 2010; 51: 741–47
7. Kajiyama S, Hasegawa G, Asano M et al: Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance. Nutr Res, 2008; 28: 137–43
8. Xie K, Yu Y, Pei Y et al: Protective effects of hydrogen gas on murine polymicrobial sepsis via reducing oxidative stress and HMGB1 release. Shock, 2010; 34: 90–97
9. Mihailovic M, Milosevic V, Grigorov I, et al: The radioprotective effect of alpha2-macroglobulin: A morphological study of rat liver. Med Sci Monit, 2009; 15(7): BR88–93
10. Morgan G: Radiation pneumonitis and fibrosis: mechanisms underlying its pathogenesis and implications for future research. Int J Radiation Oncology Biol Phys, 2006; 66: 1281–93
11. Reckzeh B, Merte H, Pfluger KH: Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small cell lung cancer. J Clin Oncol, 1996; 14: 1071–76
12. Yu T, Whitman G, Thames H: Clinically relevant pneumonitis after sequential paclitaxel-based chemotherapy and radiotherapy in breast cancer patients. J Natl Cancer Inst, 2004; 96: 1676–81
13. Rosai J: Acute pulmonary injury and interstitial pneumonia. In: Rosia J (ed.), Ackerman's surgical pathology, 1996; 8: 358–59
14. Boerma M, van der Wees CG, Vrieling H: Microarray analysis of gene expression profiles of cardiac myocytes and fibroblasts after mechanical stress, ionising or ultraviolet radiation. BMC Genomics, 2005; 6: 6
15. Christiansen H, Batusic D, Saile B: Identification of genes responsive to gamma radiation in rat hepatocytes and rat liver by cDNA array gene expression analysis. Radiat Res, 2006; 165: 318–25
16. Finkelstein JN, Johnston CJ, Baggs R: Early alterations in extracellular matrix and transforming growth factor β gene expression in mouse lung indicative of late radiation fibrosis. Int J Radiat Onco Biol Phys, 1994; 28: 621–31
17. Franko AJ, Sharplin J, Ghahary A: Immunohistochemical localization of transforming growth factor β and tumor necrosis factor α in the lungs of fibrosis-prone and "nonfibrosing" mice during the latent period and early phase after irradiation. Radiat Res, 1997; 147: 245–56
18. Johnston CJ, Piedboeuf B, Rubin P: Early and persistant alterations in the expression of interleukin-1α, interleukin-1α and tumor necrosis factor mRNA levels in fibrosis-resistant and sensitive mice after thoracic irradiation. Radiat Res, 1996; 145: 762–67
19. Rubin P, Johnston CJ, Williams JP: A perpetual cascade of cytokines post-irradiation leads to pulmonary fibrosis. Int J Radiat Oncol Biol Phys, 1995; 33: 99–109
20. Rübe CE, Wilfert F, Uthe D: Modulation of radiationinduced tumor necrosis factor α (TNF-α) expression in the lung tissue by pentoxifylline. Radiother Oncol, 2002; 64: 177–87
21. Claudia ER, Daniela U, Falk W et al: The bronchiolar epithelium as a prominent source of pro-inflammatory cytokines after lung irradiation. Int. J Radiation Oncology Biol Phys, 2005; 61: 1482–92
22. Javaid K, Rahman A, Anwar KN: Tumor necrosis factor-alpha induces early-onset endothelial adhesivity by protein kinase Czeta-dependent activation of intercellular adhesion molecule-1. Circulation Res, 2003; 92: 1089–97
23. Hillmann GG, Haas GP: Role of cytokines in lymphocyte functions. In: Aggarwal BB, Puri RK (eds.), Human cytokines: Their role in disease and therapy, 1995; 37–54
24. Vijayalaxmi, Reiter RJ, Tan DX et al: Melatonin as a radioprotective agent: a review. Int J Radiat Oncol Biol Phys, 2004; 59: 639–53
25. Buxton G, Greenstock C, Helman W, Ross A: Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals in aqueous solution. J Phys Chem Ref, 1988; 17: 513–886
26. Labiche LA, Grotta JC: Clinical trials for cytoprotection in stroke. NeuroRx, 2004; 1: 46–70
27. Reth M: Hydrogen peroxide as second messenger in lymphocyte activation. Nat Immunol, 2002; 3: 1129–34
28. Katherine CW, Mark TG: The hydrogen highway to reperfusion therapy. Nat Med, 2007; 13: 673–74

29. Hoesel LM, Flierl MA, Niederbichler AD: Ability of antioxidant liposomes to prevent acute and progressive pulmonary injury. Antioxid Redox Signal, 2008; 10: 973–81

30. Ito K, Ozasa H, Horikawa S: Edaravone protects against lung injury induced by intestinal ischemia/reperfusion in rat. Free Radic Biol Med, 2005; 38: 369–74

31. Kazez A, Demirbag M, Ustündag B et al: The role of melatonin in prevention of intestinal ischemia–reperfusion injury in rats. J Pediatr Surg, 2000; 35: 1444–48

32. Kouvaris JR, Kouloulias VE, Vlahos LJ: Amifostine: the first selective-target and broad-spectrum radioprotector. Oncologist, 2007; 12: 738–47

33. Dole M, Wilson FR, Fife WP: Hyperbaric hydrogen therapy: a possible treatment for cancer. Science, 1975; 190: 152–54

34. Kreipl MS, Friedland W, Paretzke HG: Time- and space-resolved Monte Carlo study of water radiolysis for photon, electron and ion irradiation. Radiat Environ Biophys, 2009; 48: 11–20

35. Minglun L, Amir A, Hermann J et al: Late treatment with imatinib mesylate ameliorates radiation-induced lung fibrosis in a mouse model. Radiat Oncol, 2009; 4: 66