Journal of Medical Imaging and Radiation Sciences 47 (2016) 49-54

Journal of Medical Imaging and Radiation Sciences

Journal de l'imagerie médicale et des sciences de la radiation

www.elsevier.com/locate/jmir

Research Article

Radioprotective Effects of Amifostine and Lycopene on Human Peripheral Blood Lymphocytes In Vitro

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ABSTRACT

Background: Radiation protection is a pivotal challenge for radiation workers employed in medical fields, industry, and also space professionals with an increasing role in medical diagnostic and therapeutic applications. Radioprotective effects of amifostine and lycopene and their ability to moderate the level of radiation-induced chromosomal aberrations were investigated using the dicentric chromosome assay.

Methods: Parallel human whole blood samples, pretreated with amifostine (250 μg/mL), lycopene (5 μg/mL), and/or their combinations were irradiated for 30 minutes with ^{60}Co γ rays (1, 2, 3, and 4 Gy) with a dose rate of 98.46 cGy/min at SAD = 100 cm, in vitro and cocultured with control groups. The frequencies of chromosomal aberrations in the lymphocyte of the cells were analyzed.

Results: There were no apparent chromosome aberrations in controls and also in the drug-treated groups in the absence of radiation. Radiodrug treatment significantly decreased frequency of the radiation-induced chromosome aberrations compared with radiation alone ($P < .05$). Amifostine reduced the frequency of radiation-induced dicentrics by 15.8%, 21.9%, 4.5%, and 11.6%, with dose protection factors (DPFs) of 1.2 ± 0.02, 1.3 ± 0.1, 1.05 ± 0.03, and 1.13 ± 0.02. Lycopene reduced the frequency by 17.2%, 3.07%, 1.63%, and 16.6%, with DPFs of 1.21 ± 0.12, 1.03±0.05, 1.02±0.03 and 1.12±0.03. The combination treatment reduced the frequency by 28%, 24.9%, 9%, and 31.2%, with DPFs of 1.38 ± 0.06, 1.33 ± 0.06, 1.09 ± 0.02, and 1.45 ± 0.03 with radiation doses of 1, 2, 3, and 4 Gy, respectively.

Conclusions: It can be suggested that pretreatment with combined amifostine and lycopene may reduce the extent of ionizing radiation damage in cells.

RÉSUMÉ

Contexte : La radioprotection est un défi crucial pour tous les travailleurs exposés aux rayonnements en médecine et dans l'industrie, ainsi qu'aux professionnels des vaisseaux spatiaux et a un rôle croissant dans les applications de diagnostic médical et de thérapie. Les effets radioprotecteurs de l'amifostine et du lycopène ainsi que leur capacité de modérer le niveau d'aberrations chromosomiques induit par le rayonnement ont été étudiés à l'aide de l'essai des chromosomes dicentromériques.

Méthodologie : Des échantillons de sang humain entier parallèles prétraités à l'amifostine (250 μg/ml), au lycopene (5 μg/ml) et/ou a une combinaison des deux pendant 30 minutes ont été irradiés aux rayons γ de ^{60}Co (1, 2, 3 et 4 Gy) avec un dosage de 98,46 cGy/min à SAD=100 cm, in vitro et co-cultivés avec des groupes de contrôle. La fréquence des aberrations chromosomiques dans les lymphocytes des cellules a été analysée.

Résultats : Il n'y avait pas d'aberrations chromosomiques dans les groupes de contrôle, non plus que dans les groupes traités n'ayant pas été irradiés. Le traitement a permis de réduire de façon significative la fréquence des aberrations chromosomiques induit par le rayonnement en comparaison des échantillons non traités ($p<0,05$). L'amifostine a réduit la fréquence de dicentromérisme induit par le rayonnement de 15,8 %, 21,9 %, 4,5 % et 11,6 %, avec un facteur de protection de la dose (FPD) de 1,2 ± 0,02, 1,3 ± 0,1, 1,05 ± 0,03 et 1,13 ± 0,02. La réduction associée au lycopène a été de 17,2 %, 3,07 %, 1,63 % et 16,6 % avec un FPD de 1,21 ± 0,12, 1,03 ± 0,05, 1,02 ± 0,03 et 1,12 ± 0,03, tandis que le traitement combiné a permis une réduction de 28 %,24,9 %, 9 % et31,2 %, avec un FPD de 1,38 ± 0,06, 1,33 ± 0,06, 1,09 ± 0,02 et 1,45 ± 0,03 à des doses de rayonnement 1, 2, 3 et 4 Gy respectivement.

Conclusion : Le traitement préparatoire combinant l'amifostine et le lycopène pourrait permettre de diminuer l'étendue des dommages cellulaires causés par le rayonnement ionisant.

The author(s) has no financial disclosures or conflicts of interest to declare.

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http://dx.doi.org/10.1016/j.jmir.2015.10.006

Keywords: Amifostine; chromosome aberration; ionizing radiation; lycopene; lymphocytes; radiochemotherapy

Introduction

Certain human populations have a potentially increased risk for adverse health effects due to exposure from ionizing radiation, such as victims of nuclear fallouts and nuclear terrorism, workers in the nuclear power industry, waste clean-up crews, people living in homes surrounding nuclear plants or research laboratories with radiologic facilities, patients undergoing routine diagnostic or therapeutic radiation treatment procedures, astronauts occupationally exposed to cosmic radiation, and members of the armed forces [1–4].

Ionizing radiation causes a variety of changes depending on the absorbed dose, duration of exposure, interval of exposure, and sensitivity of the tissue. Radiation damages the DNA by direct interaction and also by indirect interaction with the surrounding water molecules of the hydration shell of the DNA, which in turn damages the DNA [5, 6]. Radiation therapy is a common method for cancer therapy, but it cannot discriminate normal tissues from cancer cells and therefore may give rise to undesirable effects on normal tissues [7–9]. The use of ionizing radiation in cancer therapy may lead to temporary and/or permanent injury to the normal tissues within the treatment field. The magnitude of damage depends both on the volume of the irradiated tissue and the dose of radiation delivered [10, 11]. To increase the therapeutic index of radiation therapy, various modes of radioprotection have been developed that selectively reduce the cytotoxic effects to the normal tissues [12]. Despite the use of modern techniques for radiation dose delivery adjusting and precisely determining tumor volume, radiation therapy still induces side effects in normal tissues [13–16]. Molecules with radical scavenging properties are particularly promising as radioprotectors [17, 18]. A radioprotector can be helpful in protecting normal tissues from the deleterious effects of radiation, making it possible to apply higher treatment doses of radiation. The most effective compound studied for its radioprotective efficacy is amifostine (WR-2721, ethyol), S-2-3-amino-propylamino ethyl-phosphorothioic acid. According to preclinical studies, amifostine protects normal tissues from the cytotoxic effects of ionizing radiation. It is a prodrug that is dephosphorylated in the tissue by alkaline phosphatase to a free thiol, the active metabolite WR-1065 [19–23]. The protection of cells by WR-1065 is thought to occur through scavenging oxygen-derived free radicals and hydrogen donation to repair damaged target molecules [24, 25]. Although amifostine is the best-known radioprotector and cytoprotector that has been incorporated into general oncology practice, it still has a number of undesirable side effects, severe enough to limit the effective dosage [26, 27]. As a whole, chemical radioprotectors not only reduce radiation side effects but also may induce a number of unwanted effects on humans, including increased blood pressure, vomiting, nausea, and local and generalized cutaneoreactions [28, 29]. These disadvantages led to concern regarding botanical radioprotectants as an alternative [30].

Epidemiologic studies have emphasized the importance of consuming fruits and vegetables. Carotenoids are present in considerable amounts in plasma and human tissues and may have specific functions in relation to their high antioxidant capacities [31]. Carotenoids have been found to decrease the potential stress of oxygen-reactive species in aerobic metabolism [32, 33]. In vitro studies have shown that lycopene has the highest antioxidant capacity, which is able to quench singlet oxygen and trap peroxyl radicals [3, 34]. Lycopene is a main carotenoid in tomato and tomato products. Tomato products have higher levels of antioxidant activity and are therefore more potent than a tomato itself to reduce the risk of oxidation-related diseases [35–38]. Tomatoes contain different compounds (eg, carotenoids, vitamin C, and flavonoids) that may account for their related antioxidant properties. In particular, lycopene, the main carotenoid in tomato products, possesses the greatest quenching ability of singlet oxygen than the other carotenoids and is effective in protecting blood lymphocytes from NO_2 radical damage [3, 39]. There are also studies showing that tomato intake has been negatively related to development of some types of cancer [35, 36]. Lycopene is a nonchemical antioxidant with the least side effects. It is abundant in tomatoes and is easy to access at low price; all these features make lycopene a favorable botanical-based radioprotectant [31, 40].

There are numerous methods to evaluate the effects of ionizing radiation and also radiation moderators on cells. Dicentric (DC) chromosomes are markers of choice for the evaluation because they are easily identified, are quite specific to radiation, have a low background frequency, and show a reproducible response relationship [41–43]. There are several requirements for radiation biodosimetry: being specific to ionizing radiation, having a low background level, direct relationship with dose and radiation quality, being noninvasive, having a good reproducibility, comparability of in vitro and in vivo results, and possibility of interlab and intralab validation. Therefore, DC assay is considered "gold standard" in radiation biodosimetry [44, 45]. Bender et al published a study involving the practical use of chromosomal aberration analysis to quantify radiation injury to eight individuals exposed to gamma rays and neutrons during a nuclear excursion [46]. The utility of cytogenetic assays for assessing dose in radiation mass causalities and guiding treatment decisions has been demonstrated in Chernobyl, Goiania, Brazil, and Tokaimura in Japan [46]. This study has investigated the effects of