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Review Article

FLASH Radiation Therapy Vs. Conventional Radiation Therapy: Mechanisms and Potential Improvement of Their Differential Effects on Normal and Cancer Cells

Kedar N Prasad[1]* and Stephen C Bondy[2]

[1]245 El Faisan Drive, Engage Global, Inc.

[2]Department of occupational and Environmental Health, and Department of medicine, University of California, Irvine, CA 92697, USA.

Correspondence

Kedar N Prasad, PhD,

245 El Faisan Drive, Engage Global, Inc., San Rafael, CA 94903, Cell: 415-686-6251.

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Abstract

Conventional radiation therapy (CONV-RT) causes tumor regression, but it damages normal tissues. A novel radiation delivery technology called FLASH radiation therapy (FLASH-RT) which involves irradiation of tumor tissues at an ultra-high dose rate compared to the (CONV-RT) dose rate. Both forms of radiation therapy produced a similar tumor response, but only FLASH-RT reduced damage to normal tissue. FLASH-RT induces a transient hypoxia in cancer tissue and normal tissue. Since hypoxia is not present before irradiation, this cannot contribute to protection of normal tissues. The exact mechanisms of protection of normal tissue are unknown. Several hypotheses which include more efficient removal of hydroperoxides (ROOH), and repair ability of DNA, self-annihilation of long-lived organic radicals, and surviving functioning immune cells and stem cells have been proposed. Since higher dose rate produces greater damage, FLASH-RT should have caused a better tumor response than CONV-RT, but it did not. The reasons for this inconsistent observation are unknown. Since cancer cells require glucose and glutamine for their survival and proliferation, and since therapeutic doses of antioxidants block their uptake and metabolism, we suggest that supplementation with a micronutrient mixture containing therapeutic doses of multiple antioxidants may improve the tumor response of FLASH-RT by selective death of cancer cells, while protecting normal cells. Bystander effects of radiation therapy is a well-established observation. This issue has not been raised for FLASH-RT, but the risk exists. Preventive doses of the same antioxidants may reduce the risk of bystander effects of FLASH-RT.

Keywords

Ultra-dose rate irradiation, Transient hypoxia, Normal tissue protection, Therapeutic dose antioxidants, Glucose, Glutamine uptake.

INTRODUCTION

Conventional radiation therapy (CONV-RT) alone or in combination with chemotherapeutic agents is widely used in the treatment of human cancers. These therapies inhibit the growth of cancer cells, but they also produce acute and late effects such as recurrence of primary tumors, development of a new cancer, and non-neoplastic disease such as necrosis of the brain and muscles [1,2]. Therefore, the goal of Radiation Oncologists has been to reduce damage to the normal tissues during radiation therapy.

An established radiobiological concept suggests that higher the dose rate greater is the damage [1,3]. This concept was challenged as early as in 1947 when it was demonstrated that Chinese hamster corneal epithelial cells in culture irradiated at an ultra-high dose rate of x-ray of 4 $x10^8$ rad/s showed less chromosomal damage than that produced by a lower dose rate of $1x10^6$ rad/s. This reduction in chromosomal damage was attributed to ultra-high dose rate-induced partial hypoxia [4,5]. This suggestion presumes that hypoxia was present before irradiation, but it is induced during irradiation. Similar observations were made on Hela cells and Chinese hamster ovary cells in culture on the criteria of survival [6,7]. Hela cells are cancer cells. If an ultra-high dose rate protects cancer cells in culture, this could have an adverse effect on tumor control in vivo. On the other hand, irradiation of bacteria growing in an anoxic environment with an ultra-high dose rate at 100-299 Gy/2s increased radiosensitivity [8], which is opposite to that expected. The mechanisms of increased radiosensitivity of bacteria under anoxic condition remain unknown.

In 2014, a novel radiation delivery technology called FLASH radiation therapy (FLASH-RT) which

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can irradiate tumor and normal tissues in vivo at an ultra-dose rate of 40 Gy/s or more compared to conventional radiation therapy (CONV-RT) dose rate of 0.01 Gy/s or more was developed. Using lung cancer transplanted athymic mice as an experimental model, it was demonstrated that both FLASH-RT and CONV-RT reduced the growth of tumor to the same extent, but CONV-RT caused lung fibrosis and acute apoptotic cell death of muscle and epithelial cells, whereas FLASH-RT did not [9]. Pre-clinical studies on mice, mini pig, and cat further confirmed the advantage of FLASH-RT over CONV-RT in protecting normal tissues including the brain [10-13], the skin [14], and the blood [15]. The first clinical study with FLASH-RT was conducted on 75-year-old patients with multi-resistance CD30+ T cell cutaneous lymphoma metastasized throughout the whole skin surface. Results showed that FLASH-RT reduced tumor growth, while protecting the skin [16].

The mechanisms of FLASH-RT-induced protection of normal tissues have not been fully resolved. Proposed suggestions include more efficient removal of hydroperoxides (ROOH) and repair ability of DNA, self-annihilation of long-lived organic radicals, Fenten-effect, production of transient hypoxia, and increased number of surviving functioning immune cells and stem cells [17-20]. We suggest that transient hypoxia is not directly involved in protecting the normal tissue, because it does not occur prior to irradiation.

The objectives of this review are (a) to review FLASH-RT induced damage to tumor tissue while reducing damage to normal tissues and in comparison to CONV-RT which produces a similar tumor response but does not protect normal tissues. (b) suggested mechanisms of normal tissue protection by FLASH-RT, (c) propose how to improve tumor response of FLASH-RT while protecting normal tissue, and (d) elucidate potential damage to normal tissues caused by bystander effects of FLASH-RT and propose a plan to reduce this damage.

Why do FLASH-RT and CONV-RT Produce Similar Tumor Response despite Huge Difference in Dose Rate?

An established radiobiology concept is that higher the dose rate of low LET (linear energy transfer) radiation greater is the damage. Therefore, FLASH-RT should have caused a greater tumor response than CONV-RT, but it did not. No explanation has been suggested to resolve this inconsistency. Since the dose rate used by CONV-RT does not deplete oxygen from tumor tissue, it is likely that damage to the tumor tissue is caused primarily by oxygen-derived free radicals. On the other hand, an ultra-high dose rate used by FLASH-RT depletes oxygen; therefore, damage to the tumor tissue is primarily caused by ionization of molecules such as DNA which is not easily repaired. It appears that both forms of radiation therapy reduce tumor growth by a different mechanism. This could in part explain the similarity of tumor response between FLASH-RT and CONV-RT. The proposed explanation does not violet the major principle of radiobiology.

Proposed Hypothesis to Increase Tumor Response of FLASH-RT While Protecting Normal Tissues

Protection of normal tissue during FLASH-RT remains the most significant discovery [9-14], despite a few investigations not confirming this observation. This novel technology of delivering radiation dose to patients with cancer at an ultra-dose rate should have significant impact in enhancing the patients care. Both FLASH-RT and CONV-RT have produced a similar tumor response, the major benefits of FLASH-RT being the protection of normal tissues. If the tumor response to FLASH-RT can be enhanced, while maintaining the protection of normal tissues, it would further improve the utility of this new technology of radiation therapy in the treatment of cancer. We propose that therapeutic doses of antioxidants would enhance the cell killing effects of FLASH-RT while maintaining protection of normal tissues. Evidence to support this proposed hypothesis is briefly presented here.

Therapeutic Doses of Antioxidants kill Cancer Cells but not Normal Cells

FLASH-RT kills cancer cells, while reducing the damage to normal tissue. Several studies in experimental models of cancer cells in culture and animal models of cancer have demonstrated that therapeutic doses of antioxidants kill cancer cells, but not normal cells. For example, therapeutic doses of vitamin C and d-alpha-tocopheryl succinate inhibited the growth of cancer cells without significantly affecting the growth of normal cells, and enhanced the growth-inhibitory effects of x-irradiation and chemotherapeutic agents on cancer cells without affecting the growth of normal cells in culture and in animal models [21-26]. Therapeutic doses of other antioxidants also enhanced radiation- and chemotherapeutic agent-induced growth-inhibition and apoptosis in cancer cells without affecting the growth of normal cells [27-31]. The mechanisms of differential effects of therapeutic doses of antioxidants on the survival of cancer cells and normal cells are unknown. The question arose whether tumor cells require specific nutrients for their survival and growth, and whether therapeutic doses of antioxidants block them causing death of tumor cells by starvation. While searching for nutritional requirement for the survival and proliferation of cancer cells, we found that both glucose [32] and glutamine [33] are required for the survival and proliferation of cancer cells.

Glucose and Glutamine Requirement for the Survival and Proliferation of Cancer Cells

Glucose

Cancer cells require energy for the survival and growth; however, they use inefficient system, glycolysis, which converts one molecule of glucose to 2 molecules of ATP. This contrasts with the oxidative phosphorylation pathways used by normal cells which coverts one molecule of glucose to 36 molecules. Therefore, cancer cells require much more glucose than the normal cells to generate enough energy for their survival and growth. Cancer cells exhibit upregulation of glucose transporters GLUT-1 and GLUT-3 that increase the uptake of glucose. Because of an inefficient system of converting of glucose into energy, high levels of glucose accumulate in cancer cells. Oxidation of glucose produces excessive amounts free radicals which are required for the proliferation and metastasis of cancer cells [34]. Inhibition of glucose transporters may increase the death of cancer cell by inhibiting the uptake of glucose [35].

Glutamine

Glutamine, a non-essential amino acid, is essential for the survival and proliferation of cancer cells. Glutamine is used for synthesizing several vital molecules that are essential for the survival and proliferation of tumor cells [36]. Deprivation of glutamine may cause death of cancer cells [37,38]. Glutamine promotes synthesis of glutathione which can protect cancer cells from oxidative damage, and thereby, participates in their resistance to standard tumor therapy and in their progression [39]. Therefore, inhibition of uptake or metabolism of glutamine would cause death of tumor cells. In addition, increased expression of glutamine synthetase which enhances the levels of glutamine in

cancer cells causes them to become resistance to radiation therapy because of enhanced DNA repair ability [40]. Conversely, inhibition of glutamine synthetase in cancer cells can lead to death of cancer cells [41]. Reducing the availability of glutamine promotes radiosensitivity on cancer cells [42].

Therapeutic Doses of Antioxidants inhibit the Uptake of Glucoses and Metabolism of Glutamine in Cancer Cells but Not in Normal Cells

We proposed that therapeutic doses of antioxidants may block the uptake of glucose and metabolism of glutamine in cancer cells leading to their death. Indeed, antioxidants inhibit the uptake of glucose and glutamine metabolism in cancer cells. Few studies in support of this hypothesis are briefly described here.

a. In human colorectal cancer cells in culture, which had become resistance to standard cancer therapies, treatment with therapeutic doses vitamin C inhibited glycolysis, creating an energy crisis in the tumor cells leading to cell death [43-45].
b. Administration of alpha-lipoic acid reduced glucose uptake and inhibited the growth of neuroblastoma cells and breast cancer cells in culture. Similar observation was made on mice with transplanted breast cancer [46].
c. Treatment with quercetin blocked the uptake of glucose leading to inhibition of glycolysis, causing growth inhibition of tumor cells in culture and reduced growth and metastasis in animal model [47]. Quercetin treatment also reduced glucose uptake in estrogen receptor-positive (MCF-7) and estrogen receptor-negative (MDA-MB-231) breast cancer cells in culture [48,49].
d. Treatment with both quercetin and epigallocatechin (EGCG) also inhibited the uptake of glucose and reduced the growth of estrogen receptor (ER)-positive (MCF7) and ER-negative MDA-MB-231 breast cancer cells in culture [50].
e. Administration of resveratrol-loaded polymeric nanoparticles reduced glucose metabolism and inhibited the growth of colon cancer cells in culture (CT26 cell line) and in CT26 colon cancer cell transplanted mice [51].
f. Resveratrol induced apoptosis in ovarian cancer cells in culture by inhibiting the uptake of glucose [52,53]. Treatment with resveratrol reduced glucose uptake and glycolysis in breast cancer cells in culture and reduced the growth of tumor in mice carrying Lewis Lung carcinoma, HT-colon cancer, and breast cancer cells (T47D) [54].
g. Curcumin treatment inhibited glucose uptake and lactate production in varieties of cancer cells and reduced their growth [55]. It also prevented high glucose-induced chemoresistance by blocking the uptake of glucose [56].
h. Alpha-lipoic acid reduced proliferation of varieties of cancer cells by inhibiting uptake of glucose and lactate production. It also suppressed the growth of breast cancer cells (SKBr3) transplanted in nude mice [46].
i. Vitamin D3 treatment inhibited glutamine uptake and reduced the growth of human breast cancer in culture [57].
j. Both resveratrol and cisplatin treatment individually enhanced the levels of DNA double-strand breaks in hepatoma cells in culture, and the combination of two produced more than additive damage to DNA. Resveratrol treatment inhibited glutamine metabolism, and this may explain its enhancement of the growth inhibitory effect of cisplatin on hepatoma cells [58].
k. Curcumin treatment in combination with cisplatin suppressed proliferation of colon cancer cells in a synergistic manner. In addition, curcumin treatment overcame cisplatin resistance colon cancer cells by inhibiting the uptake of glutamine [59].

We have proposed that a mixture of micronutrients containing therapeutic doses of multiple antioxidants alone or in combination with standard or experimental therapies for increased reduction of tumor growth without affecting the growth of normal cells have been proposed [60]. This proposed mixture contains therapeutic doses of vitamin A, vitamin C, vitamin D3, vitamin E (as d-alpha-tocopheryl succinate, R-alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, and natural beta-carotene. In addition, the mixture also contains all B-vitamins, and minerals selenium and zinc at the levels of preventive doses.

Most solid tumors have varying amounts of hypoxic cells which are very resistant to radiation therapy and chemotherapy therapy. Inhibition of glucose and glutamine by therapeutic doses of antioxidant would create more serious energy crisis than oxygenated tumor cells. Oral supplementation with the proposed mixture of therapeutic doses of antioxidants 2 days before FLASH-RT and continue 2 weeks after therapy would kill more hypoxic cancer cells as well as oxygenated cancer cells compared to FLASH-RT alone, while maintaining protection of normal tissues. Clinical study is needed to test the validity of this hypothesis.

Definition of Therapeutic and Preventive Doses of Antioxidants

Some examples of therapeutic doses of antioxidants in humans are mentioned here. Vitamin C doses 5g/day or higher, vitamin E succinate doses 1600 IU or higher, vitamin A 10,000 or higher, resveratrol 1000 mg or higher would be considered a therapeutic dose. On the other hand, Preventive doses of vitamin C would include 500 mg or less, vitamin A, 5000 or less, vitamin E 60 mg or less, and resveratrol 50 mg or less.

Potential Bystander effects of FLASH-RT on Normal Tissue and their Causes

Bystander effects of radiation are observed when normal cells, which are adjacent to irradiated cells or are remote from the direct site of irradiation, sustain damage. The existence of radiation-induced bystander effect and its mechanisms of damaged has been reviewed [61]. The significant of this effect after radiation therapy was shown by the following observations:

a. Addition of the serum from survivors of Chernobyl nuclear explosion or from cancer patients who survive radiation therapy to non-irradiated cells in culture from the same individual caused chromosomal damage [62].
b. Radiation therapy of prostate cancer produced lung cancer, melanoma, and sarcoma [63].
c. Radiation therapy for rectal, cervical, and ovarian cancer markedly enhanced the incidence of lung cancer [64-66]. The mechanisms of action of bystander effect include release of pro-inflammatory cytokines such as IL-6 and TNF-alpha from the irradiated cells, and formation of long-lived free radicals, which migrate to the tissues away from the site of irradiation and cause mutation, genetic instability, and chromosomal damage [61,67].

Radiation-induced bystander effect has not drawn any attention after FLASH-RT. It has been demonstrated that FLASH-RT causes damage to cancer tissues which would release pro-inflammatory cytokines and long-lived free radicals that can cause mutation, genetic instability, and chromosomal damage in normal cells adjacent to or away from the irradiation site. Consequently, the risk of cancer in

organs away from the site of irradiation exists. We suggest that daily supplementation with the proposed mixture of micronutrient at preventive doses after completion of FLASH-RT may protect against bystander effect of therapy. Pre-clinical and clinical studies are needed to test the validity of proposed hypothesis.

CONCLUSION

Pre-clinical and limited clinical studies suggests that FLASH-RT, which delivers radiation dose at an ultra-high dose rate produced tumor response like that caused by CONV-RT at a lower dose rate, but it protected normal tissues, while CONV-RT did not. FLASH-RT induces a transient hypoxia in cancer tissue and normal tissue. Since hypoxia is not present before irradiation, this cannot contribute to the protection of normal tissues. The mechanisms of protection of normal tissue remain to be fully clarified. Several hypotheses which include more efficient removal of hydroperoxides (ROOH) and repair ability of DNA, self-annihilation of long-lived organic radicals, and surviving functioning immune cells and stem cells. Since higher dose rate is known to produce greater damage. FLASH-RT should have caused a better tumor response than CONV-RT, but it did not. No explanation has been suggested for this inconsistent observation. FLASH-RT causes damage to cancer cells primarily by ionization of molecules such as DNA, while CONV-RT produces damage primarily by oxygen-derived free radicals. We have proposed a novel plan to enhance the FLASH-RT-induced tumor response while protecting normal tissues. Cancer cells require glucose and glutamine for their survival and proliferation. We propose that supplementation with a micronutrient mixture containing therapeutic doses of multiple antioxidants, which prevent uptake of glucose and metabolism of glutamine in cancer cells, may improve tumor response of FLASH-RT by causing selective death of cancer cells. Bystander effects of radiation therapy is a well-established observation. This issue has not been raised for FLASH-RT, but likelihood of occurring of bystander effects exists. We propose that preventive doses of the same micronutrient mixture may reduce the risk of bystander effects of FLASH-RT.

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