BIOLOGICAL EFFECTS OF LOW LEVEL EXPOSURES TO IONIZING RADIATION: THEORY AND PRACTICE

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ABSTRACT

This paper briefly reviewed recent reports on the epidemiological and experimental data on low dose radiation effects which support the concept of radiation hormesis. These reports point to the possibility of existence of a threshold dose in cancer induction by ionizing radiation and in some cases the occurrence of hormetic effects with stimulation of host defense mechanisms. The possibility of the use of low dose radiation in cancer treatment to improve the outcome of conventional radiotherapy was raised by citing previous reports on experimental studies which showed increased efficacy in tumor control with significant reduction of total dose of radiation when low dose radiation was used in the combined treatment protocol.

INTRODUCTION

The concept of hormesis has gradually been accepted in the field of toxicological and radiological sciences. The first International Conference on Radiation Hormosis held at Oakland CA, USA in 1985[1] and TD Luckey's book "Radiation Hormosis" (1991)[2] have given great impetus in stimulating research work on biological effects of low level exposures to ionizing radiation at molecular, cellular, tissue and systemic levels. The scientific data in radiation biology in this aspect accumulated in the last 20 years are very convincing. With the accumulation of scientific evidence supporting the concept of radiation hormesis as a general phenomena in radiological sciences, the problem of its possible application in the field of health care has become more and more pressing. This article briefly reviews publications in recent 5 years concerning the beneficial health effects of low level exposures to ionizing radiation and possible application of low dose radiation in the treatment of cancer.

BASIC RESEARCH

DNA damage induced by ionizing radiation, directly or via ROS, is considered to be an important step in the development of various lesions including cancer formation. Recent studies have confirmed previous observations on stimulation by low dose radiation (LDR) of natural defense mechanisms including anti-oxidant formation and repair of DNA double strand breaks (DSBs).[3] Using γ-H2AX as a measure of DNA-DSBs it was found that after low dose radiation growing human fibroblasts could repair DNA-DSBs completely to the level of unirradiated control.[4] Observations on human lymphocytes after CT scan of thorax or abdomen with radiation doses in the range of 3-30 mGy showed that the γ-H2AX foci increased dose-dependently in this dose range and the lesions were completely repaired within 24 h.[5] Of course, the disappearance of γ-H2AX foci does not necessarily mean that no misrepaired lesions remian. And these misrepried lesions may later on become the source of genomic instability and neoplastic transformation. Therefore, the influence of LDR on neoplastic transformation has become a subject of concern. Recent experimental studies have shown that LDR could reduce the frequency of mutations induced by high dose radiation, and LDR could even decrease the rate of chromosome inversions produced by high dose radiation when acting after the latter.[6,7] Further experiments showed that LDR reduced the rate of neoplastic transformation to below spontaneous level.[8] Low energy (28 kVp) low dose radiation used in mammography does not increase the frequency of neoplastic transformation at doses of 0.5 to 220 mGy, and doses of 0.5 to 11 mGy reduce the neoplastic transformation rate to below spontaneous level.[9] There existed a threshold even for the neoplastic transformation induced by high energy protons and doses <100 mGy of this high energy radiation could suppress the transformation rate.[10] The mechanisms of the low dose effect have not completely been clarified, and preliminary studies suggest that it may be related to DNA repair, since 3-aminobenzamide, an inhibitor of poly-ADP-polymerase, could reverse the suppressive effect of 50 mGy on neoplastic transformation.[11]

Recent research has refuted the concept that cancer is a disease of single cells. It is now clear that the development of cancer depends on intercellular reactions in the tissue and is influenced by defense and adaptive mechanisms in the complex organism. The intercellular reactions in the local tissue involve fibroblasts, immune and inflammatory cells as well as cytokines related to them, especially the action of TGF-β (transforming growth factor-β), adhesion molecules (integrins) in the promotion of cancer development.[12-15] Recent studies have shown that the integrity of normal tissue structure plays an important role in the suppression of the carcinogenic effect of oncogenes. For example, it has been observed in 3-D culture of mammary cells that the integrity of the mammary epithelial structure suppresses the carcinogenic effect of c-Myc gene and the maintenance of this tissue integrity is related to LKB1 gene,

so that deletion of LKB1 leads to destruction of the integrity of tissue structure and appearance of cancer-like cells.[16] Therefore, it is envisioned that "normal cells unite against cancer" and, if they fail, cancer cells will "hijack" normal cells (including fibroblasts, immune cells, etc.) to favor their proliferation and invasion. High doses of radiation change soluble and insoluble elements of tissue microenvironment and thus affect cell phenotype, tissue structure, intercellular physical relations and signal transduction. The mechanisms of these microenvironment changes induced by high dose radiation include persistent action of chronic inflammation and TGF-β.[17] At the same time high doses of radiation suppress the immune surveillance against cancer while low doses of radiation activate anticancer immune functions.[18,19]

Radiation bystander effect is a phenomenon which has attracted the interests of radiobiologists. The first observation was made with microbeams of α particles irradiating a small portion of cultured cells resulting in damage in the unirradiated "bystander " cells. The mechanism of such effects is related to signals passed from the irradiated cells to the unirradiated cells directly via gap junction-mediated intercellular communication between cell contacts or signal molecules released from the irradiated cells into the microenvironment, e.g., NO, TGFβ, etc. It means that not all lesions in the cells are produced by the traversal of radiation through the "target". With the discovery of this phenomenon it was once argued that the linear no-threshold model may underestimate the risk of health effects of radiation. However, when cultured C3H10T1⁄2 cells were pre-irradiated with 20 mGy of γ-rays 6h before the hit of α particles, an adaptive response was observed manifested as increase of survival by 75%. It was thus thought that α particles chiefly cause damage and low dose γ-rays induce adaptive response.[20,21] There are also recent studies showing that LDR-induced bystander effect may be manifested as apopstosis, thus eradicating the cells with genomic instability and lowering the frequency of neoplastic transformation. Such a phenomenon was called apoptosis-induced protective effect.[22,23] Furthermore, signals from low dose-irradiated non-transformed cells could cause apoptosis of transformed cells.[24] Therefore, radiation bystander effect can either cause damaging effect or give rise to adaptive response, depending on the actual condition. There also exists a threshold for the induction of bystander effect, for human skin cells the threshold dose of γ-rays being 2 mGy. The threshold dose for different species may vary greatly, and genetic or epigenetic background may be more important than the irradiation dose in the induction of bystander effect.[26,27] For example, bystander signals for apoptosis could be induced by irradiating C57BL/6 mice, but not CBA/Ca mice.[28]

CANCER PREVENTION BY LOW LEVEL RADIATION

Recent reports on epidemiological surveys have shown beneficial health effect of low level exposures to ionizing radiation expressed as decreased cancer mortality and/or all-cause mortality as well as increased life span (longevity). Examples of these are the Hanford downwind inhabitants 50 years' survey,[29,30] the Chernobyl contaminated area 20 years' survey,[31] the US nuclear shipyard workers study (NSWS) of more than half a century,[32,33] the British radiologists 100 years' observation[34] and the British nuclear workers 51 years' study.[35,36] These population studies are supported by laboratory research. It was found that for the induction of thymic lymphoma in normal mice by γ-rays there existed a threshold dose of less than 1 Gy since doses within 1 Gy of γ-rays did not increase the occurrence of lymphoma above the basal level, and after irradiation with 5 Gy the incidence of lymphoma increased to 12.5%. Even in SCID mice, which have defect in DNA-DSB repair and immune deficiency, there exists a threshold dose of 0.1 Gy for induction of thymic lymphoma. Irradiation with this dose does not increase the occurrence of lymphoma above the spontaneous rate of 31.7% and irradiation with 0.25 Gy and 2 Gy increases the occurrence rate of lymphoma to 51.4% and 80.6%, respectively.[37,38]

It was further found that low dose or low level radiation could suppress the carcinogenic effect of high dose radiation. C57BL/6J mice exposed to fractioned doses of whole-body irradiation with 1.75 Gy X-rays once a week for 4 consecutive weeks with a total dose of 7.0 Gy resulted in occurrence of thymic lymphoma in 43.3% of mice within 6 months. When each fractioned dose of 1.75 Gy was preceded by whole-body irradiation with 0.075 Gy with an interval of 6 or 12h, the incidence of thymic lymphoma decreased to 15.1% and 17.1%, respectively (P<0.05), while unirradiated mice and mice receiving 4 doses of whole-body irradiation with 0.075 Gy alone did not develop thymic lymphoma within 6 months of observation.[39] When the same protocol was applied to C57BL/6J mice with the fractioned dose increased to 1.8 Gy (total dose 7.2 Gy) instead of 1.75 Gy (total dose 7.0 Gy), 90% of irradiated mice developed thymic lymphoma in 9 months, and when each high dose was preceded by 0.075 Gy, the incidence of thymic lymphoma decreased to 63%.[40] If the preceding low dose was replaced by continuous low level ^{137}Cs γ-irradiation at the dose rate of 20 μGy / min beginning 35 days before the start of the fractionated high dose and continued for 450 days, the incidence of lymphoma further decreased to 43%, while the low level radiation alone for 450 days did not cause development of thymic lympjoma. Continuously irradiated mice showed no loss of hair and a greater body weight than unirradiated controls.[40] The mechanism of the suppressive effect of low dose radiation on the carcinogenesis caused by high dose radiation is apparently related to an adaptive response induced by low dose radiation manifested as reduction of DNA damage caused by high dose radiation as well as activation of immune surveillance induced by low dose radiation.[39,40]

OPTIMIZATION OF CANCER RADIOTHERAPY WITH LOW DOSE RADIATION

Radiotherapy is one of the most commonly used clinical treatments for cancer. However, the potential for tumor control with radiotherapy must always be carefully balanced with the risk for normal tissue damage.[41,42] Large doses of radiation may over-stimulate the secretion of pro-inflammatory cytokines, including IL-12, IL-18 and

others, with the danger of promoting cancer invasion and metastasis.[12,13,43] In addition, tumor cells outside the immediate field of radiation exposure or that have metastasized to distant sites are not destroyed by local irradiation used in conventional radiotherapy. In some cases of more advanced disease, such as non-resectable lung cancer, radiotherapy in combination with chemotherapy may improve the treatment result to some extent, but the toxicity is not easily tolerated. Therefore, it has become an important issue in radiation oncology to seek for measures to decrease local radiation dose and increase anti-tumor effect. It was found that whole-body irradiation with low doses given before implantation of cancer cells (B16 melanoma and Lewis lung cancer) in mice caused retardation of tumor growth, prolongation of survival time, lowering of mortality rate and reduction of pulmonary metastasis.[44] On the basis of these observations experimental studies with the proper use of whole-body X-irradiation with low doses in combination with conventional radiotherapy were designed for the treatment of cancer in mouse models.[45] A mouse model of Lewis lung cancer was established by subcutaneous implantation of cancer cells and treatment was started 10d after cancer implantation. The protocol of local radiotherapy with 5 Gy X-rays in each session with 3 sessions in one week for two consecutive weeks (a total dose 30 Gy) caused significant suppression of tumor growth (curve B in figure 1 as compared with the untreated control in curve A). When the second and third local doses of 5 Gy in each week was substituted by whole-body irradiation with 0.075 Gy (a total dose 10.3 Gy in 2 weeks), the same degree of suppression of tumor growth was achieved as shown in curve C which overlapped with curve B. That is to say, with substitution of 4 large local doses with 4 low doses given as whole-body irradiation the same therapeutic effect was obtained at about 1/3 of the total dose.

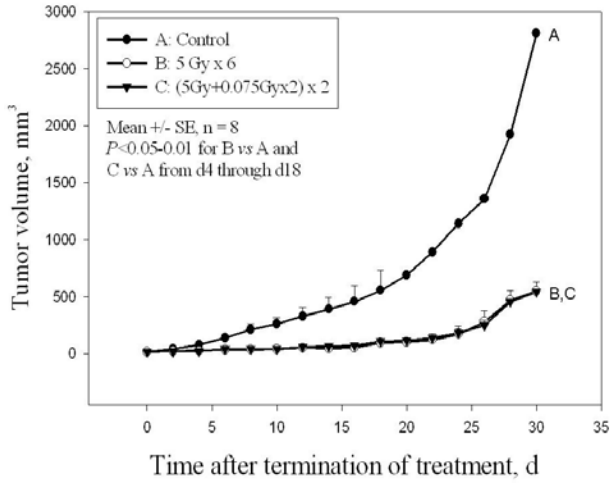

Figure 1 Lewis lung cancer in C57BL/6J mice treated by a combined regimen of local radiotherapy with 5 Gy sessions plus whole-body irradiation with low doses (adopted from reference 45)

Another protocol with 2 Gy x 6 in 2 weeks was tried to see if further improvement of treatment efficacy could be realized by combination of conventional local radiotherapy with whole-body irradiation with low doses. As seen in figure 2, 2 Gy x 6 in 2 weeks (a total dose 0f 12 Gy) could not efficiently control the tumor growth (curve B in figure 2 as compared with curve A which is the control with no treatment), while substitution of the second and third doses of local irradiation with whole-body irradiation with 0.075 Gy in each of the 2 weeks (a total dose of 4.3 Gy), tumor growth was significantly slowed down (curve C in figure 2). That is to say, by substitution of 4 local doses of 2 Gy with whole-body irradiation with 0.075 Gy, therapeutic efficacy was increased with a reduction of total dose by 2/3.

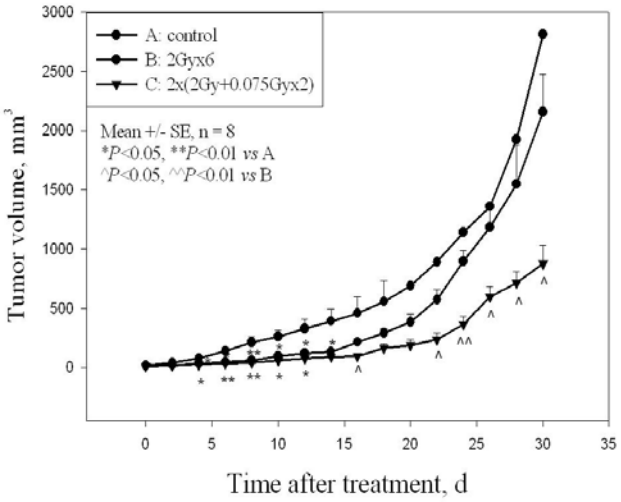

Figure 2 Lewis lung cancer in C57BL/6J mice treated by a combined regimen of local radiotherapy with 2 Gy sessions plus whole-body irradiation with low doses (adopted from reference 45)

Table 1. Comparative changes in tumor growth and progression in different groups of mice treated with different protocols of gene radiotherapy after implantation with Lewis lung cancer cells

Parameter	Group A	Group B	Group C	Group D	Group E
Mean survival time	100	121.2	161.2$^{(1,2)}$	157.7$^{(1)}$	194.1$^{(1,2,3,4)}$
Average tumor weight	100	60.8$^{(1)}$	38.3$^{(1)}$	32.7$^{(1,2)}$	17.8$^{(1,2,3,4)}$
Pumonary metastasis	100	83.3$^{(1)}$	59.5$^{(1)}$	39.9$^{(1,2,3)}$	20.9$^{(1,2,3,4)}$
Intratumor angiogenesis	100	87.9	76.2$^{(1)}$	45.7$^{(1,2,3)}$	30.9$^{(1,2,3,4)}$

Group A: tumor control with no treatment; Group B: 2Gy x 6; Group C: 2 x (2Gy + 0.075Gy x 2); Group D: 2 x (E18B + 2Gy x 3); Group E: 2 x (E18B + 2Gy + 0.075Gy x 2). Mean survival time was calculated from groups of 8 mice in each group at the end of 8 weeks from beginning of treatment. Average tumor weight, pulmonary metastasis and intratumor angiogenesis were from groups of mice, 6 in each, sacrificed 18 d after termination of treatment. All values are calculated with reference to group A as 100%. (1) $P<0.05$ *vs* A, (2) $P<0.05$ *vs* B, (3) $P<0.05$ *vs* C, (4) $P<0.05$ *vs* D. (E18B is the abbreviation of plasmid Egr-mIL-18-B7.1)

Other measures could be added to the protocols mentioned above to further increase the efficacy of cancer control. Gene therapy is one example. It is known that the early growth response 1 (Egr-1) gene is

very sensitive to ionizing radiation. Recombinant plasmids can be constructed with anticancer genes placed downstream of the promoter of Egr-1 gene in order that doses as low as 0.05 to 0.1 Gy of radiation could activate the expression of these molecules to up-regulate anticancer activity.[46,47]

It can be seen from data in table 1 that as judged from the mean survival time, average tumor weight, pulmonary metastasis and intratumor angiogenesis, there was significant improvement when low dose radiation was combined with conventional radiotherapy (compare group C with group B), and intratumor injection of the radiosensitive plasmid Egr-mIL-18-B7.1 (E18B) further increased the treatment efficacy (compare group D with group B and group E with group C). Group E in which low dose radiation was superimposed upon gene radiotherapy showed the most marked efficiency in cancer control. In this group a reduction of total radiation dose to 1/3 of control is accompanied with marked increase of treatment efficacy as shown by doubling of survival time and reduction of tumor weight and metastatic foci to around 1/5 of the control.

CONCLUDING REMARKS

The biological effect of low level exposures to ionizing radiation is a problem of much public concern. The most important health effect related to ionizing radiation is cancer risk. Ionizing radiation at medium to high doses could lead to increase in cancer incidence. However, the cancer risk of low level exposures to ionizing radiation has long been a problem of debate. When BEIR I report was released in 1972 recommending the use of a linear model for estimating radiation risks, UNSCEAR VI questioned its validity in the same year. In 2005 US National Academy of Science released the BEIR VII report and French National Academy of Science and Academy of Medical Science published a joint report on estimation of the carcinogenic effects of low doses of ionizing radiation.[49,50] The former document insisted on using the LNT model for estimation of risk for low and very low doses though it recognized the uncertainty of such judgment, while the latter questioned its validity based on recent advances in the research on biological effects of low level exposures to ionizing radiation.[51,52] In a 2007 updaie on the website of US DOE LDR Research Program support was given to the viewpoint of the French joint report according to recent advances made in experimental studies under the support of this Research Program [53]. As briefly reviewed in the present paper there has been accumulating evidence both from human population surveys and animal experiments pointing to the existence of a threshold dose for radiation carcinogenesis or even beneficial health effect from low level exposures to ionizing radiation.

The use of low dose radiation in combined regimens of cancer therapy was briefly examined with a few experimental examples indicating the possibility of improvement of treatment efficacy using properly planned protocols with the inclusion of low dose radiation. The experimental findings cited in the present paper showed that low dose whole-body irradiation in combination with local radiotherapy could improve the tumor control in mouse lung cancer model, and introduction of the radiosensitive pEgr-IL-18-B7.1 plasmid into the tumor could further promote the treatment efficacy. It is important to note that such an improvement in treatment efficacy was accompanied with a reduction of total radiation dose to about 1/3 of that in the conventional radiotherapy regimen. These experimental findings may set the stage for developing rational clinical protocols in cancer treatment.

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