CARE Radiation Therapy

Increasing Effectiveness and Reducing side effects

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Abstract

In radiotherapy, a large radiation dose must be applied to both cancer and neighboring healthy cells. Many recent experiments have shown that a low dose of ionizing radiation turns on certain protective mechanisms that allow a cell to better survive a subsequent high dose of radiation. This adaptive response has an important and positive consequence for radiotherapy. This paper describes simple changes in treatment procedures to make use of these beneficial effects. A low dose applied only to the healthy cells surrounding the tumor will produce some damage. More importantly however, it will also start the adaptive response in the cells that will yield increased protection when the large therapeutic dose is applied. The resultant immediate damage to the predosed cells will be thereby reduced as well as the probability that the high dose therapy itself will induce a subsequent secondary cancer.

The human genome project and its associated technology are leading to great advances in medical science. This new technology allows many questions to be adequately addressed for the first time. One such application is the study of the detailed cellular and molecular responses induced by low doses of ionizing radiation. Earlier technology found an adaptive response to low radiation doses but was not sensitive enough to directly measure the genetic effects of very low levels of radiation (say 0.01- 0.1 Gy = 1-10 rads). A dose of ~1 rad is delivered during a typical CT scan of the chest or abdomen. This adaptive response has been well discussed at many international conferences (see the UNSCEAR and R.E.J. Mitchel references).

There is no question that radiation can damage living cells. However, an important question still remains; can the damaging side effects from a large radiation dose, such as that utilized in cancer therapy, be reduced? It will be argued here that timing and dose control can be used to moderate damage to healthy cells without reducing the therapeutic goal, to kill cancer cells. We will make the conservative assumption that even a small dose will cause some damage.

Recent studies have shown that gene expression is very different following a low dose of radiation as compared to a high dose. A low dose activates many important genes ranging from those involved in repair of DNA and general cell damage, to those involved in apoptosis, programmed cell death. Recent studies (see references listed below) on cell cultures and biopsied human cells have shown that low doses of radiation may reduce the level of spontaneous cell transformation. The main impact of these results so far seems to be a re-examination of the linear-no-threshold hypothesis, LNT, which is used in setting the allowed dose limits for workers exposed to radiation. The possible effect on radiation risk and standards of this new knowledge is under active discussion (see references).

In this note, the author will describe the **therapeutic application of predose radiotherapy**. Recent developments such as IMRT have substantially reduced the radiation dose delivered to the surrounding healthy cells, but damage still occurs to these cells. The protective adaptive

response of cells to a predose will allow a higher dose per session, a higher kill probability, and fewer radiotherapy sessions while keeping the healthy cell damage at an acceptable value. The basic treatment concept is illustrated in Figures 1 and 2. Other treatment modalities, such as encapsulated radioactive seeds, can be pre-treated in a similar manner.

The key observation is that **the adaptive response of cells to a low dose of radiation has very different consequences for therapy than for protection**.

There is a continuing discussion as to whether radiation is harmful no matter how small the dose, or on the contrary, whether a small dose can actually be beneficial in certain circumstances. The present suggested therapy does not depend upon the final outcome of this argument. We make the conservative assumption that all radiation poses a risk, no matter how small the dose. However, the risk posed by the predose is negligible compared to the immediate threat of an active cancer and it will reduce the overall body damage. What has been clearly demonstrated in both cancer and healthy cells is that the harmful effects of a large dose of radiation can be mitigated by a prior low dose of radiation that is applied at the proper time, place, and dose. This new modification of radiation therapy is called **CARE (Cell Adaptive Response Effect) T**herapy.

In experiments performed by A. Wyrobek and others at the DOE Lawrence Livermore Lab, human lymphoblastoid cells exhibited such an adaptive response. A dose of 0.05 Gy was applied and after a wait of 6 hours, a higher 2.0 Gy dose was applied. It was found that chromosomal damage was reduced by 20-50 % compared to cells with no priming dose.

Experiments have been performed at U. C. Davis on healthy human skin cell plugs with similar protective results for the cellular adaptive response to a low radiation dose (see Z. Goldberg). In experiments performed by R.E.J. Mitchel and others at Chalk River Lab, Co60 gamma doses as low as 0.01 to 0.1 Gy protected cells against neo-plastic transformation by a subsequent large acute radiation exposure. Surprisingly a single pre-exposure of 0.001 Gy also reduced neo-plastic transformation by factor of 3-4 below the spontaneous rate. Pre-exposure doses ranging from 0.001 up to 0.1 Gy resulted in essentially the same reduction factor. [Note that a dose of 1 mGy corresponds on average to the absorption of one gamma ray photon per cell.]

Important low dose experiments on mice were carried out by Rodgers and Holmes. They showed that a low dose (~ 0.1 Gy) delivered at a very low dose rate over several weeks caused little additional damage over the control presumably because the cell repair mechanisms had time to fully act and repair the damage. The same low dose delivered at a high rate, over ~20 minutes, caused measurable damage. A subsequent high dose of ~1.5 Gy was given to a group of mice after a 24 hour delay and compared to a group subject to the same high dose without the high rate predose. The mice given the predose suffered considerably less damage than the ones denied the predose treatment.

To summarize, many experiments have shown that a small dose of radiation triggers an adaptive response that can reduce the cell damage from either a subsequent high dose of radiation or even from toxic chemotherapy agents (the possible application of this effect to chemotherapy will be discussed elsewhere). In some of these experiments, a prior dose of ~0.05 Gy was shown to considerably reduce the damage from a subsequent dose of ~2 Gy. In some published experiments, an even smaller prior dose was shown to offer protection to the same large dose of radiation. What is not yet determined is the degree and type of protection provided in the medium term and in the long term.

Further research needs to be done in order to fully exploit this proposed therapy. Of particular importance is **the time development of the effects**. There is published evidence that the protective effects take 4-6 hrs to become fully active and clearly lasts at least 24 hrs and probably longer. Its longevity can be increased by lowering the dose rate and increasing the exposure time to keep the same total predose. More experiments particularly aimed to study the therapeutic application need to be performed. Other topics needing study include the radiation induced adaptive response of different healthy cell types, such as brain, liver, muscle, etc., including cancerous cell types. There is evidence that the gene response includes DNA repair, heightened immunity, and heightened anti-oxidant production. No clear consensus yet exists on the detailed mechanisms of the observed adaptive response, but its existence is indisputable.

The following suggested treatment assumes that the adaptive response, CARE, has been fully mapped. In the simplest terms, the therapy consists of one additional step added to each sub-group of standard radiation treatment fractions. This step consists of a low dose of radiation delivered, not to the cancerous tissue, but only to the healthy surrounding cells that will inevitably receive a muchlarger dose during the standard treatment. The total additional dose of this preconditioning step is small (between 0.01 - 0.1 Gy), of the order of a few chest CT Scans. This would seem to be within the flexibility in dose afforded to radiologists in standard treatment decisions. It is important to note that this treatment is **to be used only** in situations in which healthy cells will inevitably receive a very high radiation dose in the course of subsequent treatment.

This proposed treatment relies on two basic elements, one from physics/engineering and the other from biological experiments:

- The use of computers to optimize the radiation exposure by controlling the position, timing, and intensity of the x-ray source. The predose planning can be done with present equipment software.
- The adaptive response of radiation on cells discussed above - namely that a low radiation exposure followed later by a high dose is less damaging to a cell than the total of the two exposures applied with no delay.

As discussed earlier, this latter effect is commonly interpreted by assuming that the low dose of radiation initiates repair processes in the cell which require time to become fully effective.

Since there is evidence that radiation can increase cell proliferation in tumors, a whole body dose may have the undesired effect of increasing tumor cells or in putting them in more resistant phases of the cell cycle (termed "recruitment"). However, in our proposed extra radiation step, the main cancer mass is not irradiated at all and neither is the entire body – only the healthy tissues affected by the treatment. The suggested predose can initiate several observed cell behaviors. Among these are: the mechanisms that can repair damage without error, alert the genetically determined cell death process, apoptosis, that can prevent mutated cell survival, and increase the latency period of any remaining cancers to gain lifespan.

BRIEF DESCRIPTION OF THE PROPOSED TREATMENT: The treatment consists of two major steps that follow the detection and characterization of the cancer:

(1) A low radiation dose is applied only to the normal cells surrounding the cancer. The region containing the cancerous cells receives **no** radiation.
(2) After a chosen time **delay**, several hours up to a day, a standard high radiation dose is applied to both the normal and the cancerous region, with as low a dose as possible to the healthy cells.
(3) The subsequent predose and fractionated therapy are then interspersed for

optimum protection utilizing the time dependence of the adaptive response.

These steps are schematically illustrated in two dimensions in Figures 1 and 2. Depending upon the scale of the time dependence of the adaptive cell response, step 2 may be repeated with defined time lags, while step 1 is optimally interspersed so as to take maximum advantage of this time dependence. It is essential in step 1 that the cancerous cells are not irradiated – otherwise their repair functions will be activated. Healthy cells that are too closely intermixed with cancer cells are sacrificed as in standard therapy. CARE therapy is described in detail in the patent written by the author.

It has been shown (see R.E.J. Mitchel) that the protective adaptive response is activated if the low dose is given at a low dose rate (so that the low dose stage lasts perhaps an hour or so) and then the high dose is applied soon thereafter. The resultant risk of a malignant transformation is reduced by a factor of 2-3. If this effect is proved to be sufficiently protective, it could be utilized to shorten cancer therapy by increasing the high dose per session, thereby reducing their number. Also, the low rate low dose could be given before each high dose session if the temporal development of the adaptive response is suitable. Eliminating the separate low dose session may be particularly important for veterinary applications since the animal would not have to be sedated for this extra session.

RADIATION WORKER PROTECTION via SCHEDULING: The adaptive response might be useful for improved worker protection by simply scheduling worker exposure optimally. For example, if a worker must enter a high radiation area for an extended time, they should first enter for a short period that is sufficient to trigger the adaptive response (< 0.1 Gy, perhaps ~ 0.01 Gy), exit the radiation area, and then wait (~6-24 hours) for the protective adaptive response to fully activate. They then reenter the radiation area for the remainder of their allowed exposure. Various scenarios for protecting First Responders are clearly possible.

CANCER THERAPY TRIALS: At the Virginia Tech College of Veterinary Medicine, radiation exposure of canine cancer cell cultures followed by a microarray analysis of the adaptive response has been studied using a canine gene chip (see refs.) with emphasis on time dependence. As expected, canine cells respond to a low dose similarly to human and mice cells. The treatment of 8 canine patients with selected cancers has been completed. Healthy and cancer cell samples were taken before and after treatment at different time delays for later microarray analysis. All of the canine patients have recovered well and had minimal bad side effects covering a post treatment period (see R. Blankenbecler).

SUMMARY: In modern radiotherapy, the dose applied to tissues surrounding the cancer is minimized, but is nevertheless significant. The proposed CARE therapy uses a low radiation dose applied only to these regions to suppress the damaging effects from subsequent radiation therapy. The preliminary low dose is directed to those regions of the body which are non-cancerous but which will inevitably receive a large dose during standard treatment. Ideally the cancerous region should not receive any radiation during the initial low dose step. The purpose of the low dose exposure is to turn on repair mechanisms in the healthy cells which then can increase the probability that they self-repair and survive the therapy in a normal state or suffer apoptosis if they are not repairable. The cancerous tissue does not receive the prior low dose of radiation and therefore remains sensitive to the subsequent standard large dose.

The low-dose CARE therapy can be combined with other modifications such as the use of selected drugs. However, such drugs must be extensively tested before their use on human

patients whereas low dose therapy uses a small additional radiation exposure in addition to the large dose of the well tested and well understood standard therapy. CARE can be used in several ways: (1) increase the high dose that can be tolerated, reduce the number of sessions, cost, and increase the probability of kill, (2) use the standard high dose fractions and reduce the undesirable side effects, (3) reduce the probability of a second stage cancer induced by the high dose radiotherapy and increase its latency should it develop, (4) reduce the collateral damage from a photon beam that occurs in front of and behind the cancer. Thus its resultant long term damage distribution approaches that of a proton or carbon beam (Bragg peak effect).
CARE Therapy can be used with all radiation delivery systems, among these are moving accelerator sources, Cyber Knife, Radioactive encased pellets, and Gamma Knife. The small number of sessions required by the Gamma Knife technology may provide a particularly effective application of CARE Therapy.

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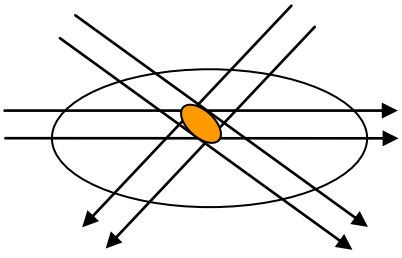

Figure 1 – Standard rotating

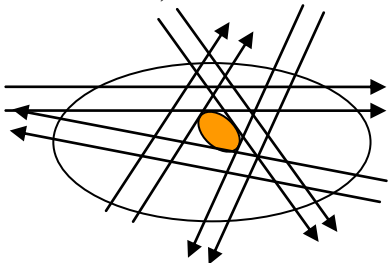

Figure 2 – Rotating low dose pre-