BioLogical review

Biological Therapies

A BIOLOGICAL THERAPIES NEWSLETTER

Radiation Therapy and Vitamin C

There is considerable confusion about whether antioxidants, such as vitamin C, should or should not be used in conjunction with radiation therapy for cancer treatment. The confusion comes about because there have been concerns expressed that antioxidants could theoretically block the effects of radiation, yet antioxidants, including vitamin C, are prescribed to alleviate the side effects of radiation therapy. Some doctors also use high doses of vitamin C (usually I.V.) as a primary cancer treatment. Despite the theoretical concern, clinical experience does not indicate that vitamin C treatment reduces the effect of radiation therapy, and there are several studies that show that vitamin C is supportive in radiation therapy and may improve the effects.

This newsletter will examine the role and effect of vitamin C before, during and after radiation therapy and challenge the notion that vitamin C may make radiation therapy less effective.

Radiation therapy and vitamin C – are they opposites?

The theoretical concern raised by medical scientists about antioxidants being used during radiation therapy is that vitamin C may have an opposite effect to the radiation. This concern arises because most cancer treatments, including chemotherapy and radiation therapy, are thought to inflict damage to cancer cells by producing large amounts of free radicals. Some free radicals can be highly destructive to biological tissues, and if these are in high enough concentration in tumor tissue then the tumor will be affected. The theoretical concern is that vitamin C or other antioxidants may react with these free radicals and reduce their ability to damage the tumor, so it is proposed that vitamin C may have an opposite effect to radiation therapy and theoretically should not be used concurrently.

It is important to note that the idea that antioxidants may reduce the effectiveness of radiation therapy is a *theoretical concern* which is based upon the assumption that radiation therapy is effective in cancer treatment *entirely* due to free radical production. The popular idea is that if large amounts of damaging free radicals are produced during radiation then various cell components will be destroyed, damaged, or rendered useless, such as the cell's DNA, membranes and internal organelles. During radiation dosing a cancer cell may be killed, or damaged to such an extent by the free radicals produced that it subsequently dies. In either situation the cell debris will presumably be removed by the immune system. Free radicals are produced in large quantities during radiation, and for some time after irradiation due to inflammatory processes. Cells continue to die for some time after radiation therapy (in some cases weeks after the radiation), *however the assumption that this continued death of cells is due to continued free radical production is probably incorrect*.

Correspondence to: Dr. Ian Dettman. PO Box 702,
Braeside VIC 3195 Australia. 61 3 9587 3948 biol@biol.com.au

Radiation kills cells via "programmed" cell death

Radiation *damages* cells directly via the production of free radicals. Although free radicals initiate the damage, it is largely the *extent and type* of the damage to the cells that determines their outcome, not necessarily an ongoing production of free radicals. Free radicals produced at the time of the radiation therapy cause damage to the cell's components, including the cell's DNA, membranes and organelles. If a cell is sufficiently damaged, various mechanisms come into play to "remove" that cell, i.e. to kill it, and these mechanisms are largely initiated by the damaged cell itself. Cells have a capacity for "programmed cell death", which is called *apoptosis*. For various reasons, cells may undergo apoptosis at any time, however after radiation therapy apoptosis appears to be the major mechanism by which cells die. If the radiation therapy is correctly targeted, this means that the death of cancer cells is largely due to apoptosis of the affected cancer cells in the hours to days after the therapy.

Moderate radiation will also produce an inflammatory response, however it takes time for this response to develop. Free radicals are always produced in the inflammatory response, *whatever the response is due to*. Immune system cells (phagocytes) "digest" cellular debris by engulfing debris into their interiors and producing large amounts of damaging free radicals to break the debris down; however this is an *internal* process inside lysosomes in the phagocytes and is quite different to the uncontrolled radical production produced by radiation. The inflammatory response does not *normally* lead to extensive cell death through apoptosis because the radicals produced

do not interact with cells the same way that radicals produced by radiation do, i.e. even quite extensive inflammatory responses do not have the “effect” on inducing apoptosis in cells like chemotherapy and radiation therapy do. Severe and uncontrolled inflammation may lead to the release of radicals from immune cells and the escalation of damage. Uncontrolled inflammatory responses damage tissues by lysing membranes and killing cells directly, however by the time the cell’s DNA is affected by these radicals the cell is most likely already dead. Removal of dead cell debris is largely via immune mechanisms, not apoptosis. Apoptosis *may* occur to some limited extent during inflammatory responses; however it is more likely that this is due to the presence of chemical immune triggers rather than free radical bombardment of the cell’s DNA. If inflammation had the same effect on inducing apoptosis as chemotherapy and radiation therapy do, then severely inflamed areas (such as a thumb hit very hard with a hammer) would be expected to "disappear" rather than heal and return to normal function.

Apoptosis is "turned on" by gene expression

The initiation of apoptosis in cells, including cancer cells, is under genetic control. If the genes in the DNA that produce the proteins and enzymes that initiate cell death are "turned on", then the death of the cell is inevitable. The "turning on" of genes is called *gene expression*, and if the genes that control apoptosis are expressed then the cell will die. Because of major damage to the cell, especially damage to parts of the cell’s DNA, radiation therapy causes these apoptosis genes to be expressed (largely, most chemotherapy regimens are believed to do the same thing), i.e. radiation "turns on" the mechanisms that ultimately cause the death of the cell.

If the DNA of the cell that contains apoptosis genes is damaged or mutated in some way, then the apoptosis mechanisms for that cell will not work properly, if at all. There is a growing body of evidence that such genetic mutations are responsible for resistance to many chemotherapeutic drugs and failure of chemotherapy treatments, i.e. the treatments won't work because the mechanisms of cell death cannot be turned on (presumably radiation therapy may also "accidentally" inactivate these genes).

One of the genes studied extensively for its role in tumor suppression by initiating apoptosis is called the "p53 tumor suppressor". Mice which do not have this gene (a "knockout" model the gene has been "knocked out" and thus the effect or non-effect of the gene can be studied closely) display very high resistance to chemotherapy and radiation therapy. Additionally, if this gene is "implanted" into p53 knockout mouse tumor cells the cells become sensitive to the therapies (1).

Another family of genes is known to influence cancer cell survival and the apoptosis response. The gene Bcl-2 produces resistance to a wide variety of toxic agents in humans if it is over expressed, by blocking apoptosis. A related gene, bax, enhances radiation sensitivity and response to chemotherapeutic drugs by promoting apoptosis, however there are several genes known to be involved in apoptotic signaling (1). The investigation of the genetic control of apoptosis is a rapidly emerging field and a very complex one at that. By no means is this area fully understood however at present it is apparent that genetic control of apoptosis vs. cell survival is at the bottom of cellular response to chemotherapy and radiation.

An excellent review of the role of apoptosis in cell death after radiation therapy and chemotherapy has been written by Clemens et al:

"The dogma that antineoplastic treatments kill tumour cells by damaging essential biological functions has been countered by the notion that treatment itself initiates a programmed cellular response. This response often produces the morphological features of apoptosis and is determined by a network of proliferation and survival genes, some of which are differentially expressed in normal and malignant cells. Correspondingly, mutations that interfere with the initiation or execution of apoptosis may produce tumour-cell drug resistance. Remarkably, many of the genes that modulate apoptosis in response to cytotoxic drugs also affect apoptosis during tumour development; hence, the process of apoptosis provides a conceptual framework for understanding how cancer genes can influence the outcome of cancer therapy. Although the relative contribution of apoptosis to radiation and drug-induced cell death remains controversial, clinical studies have associated antiapoptotic mutations with treatment failure."(1)

Vitamin C and radiation therapy

There is surprisingly little clinical research about the use of vitamin C with radiation therapy in humans; however there are NO studies that show that vitamin C makes radiation therapy less effective. *The notion that vitamin C may reduce the effectiveness of radiation therapy is purely theoretical and is without proof.* There are a number of animal studies that show clearly that vitamin C does *not* reduce the effectiveness of radiation therapy, in fact some of these studies have shown the opposite an *increased effect* if vitamin C is given with radiation therapy. Lamson et al have collated some of this information in a review (2):

"In mice, vitamin C (1 g/kg), given intraperitoneally with vitamin K3 (10 mg/kg), increased the therapeutic effect of radiation on solid tumors without causing any signs of toxicity due to the vitamins. (3)

In another mouse study, a single intraperitoneal dose of 4.5 g/kg vitamin C was not cytotoxic to normal tissue and did not change the radiation effect on tumor tissue. The lethal dose of radiation increased and skin desquamation reaction was reduced by ascorbate treatment. It should be noted that these vitamin C doses are much greater than have been used historically in humans. (4)

The radioprotection of healthy tissue and radiosensitizing effect in tumors with use of ascorbate were confirmed in two other mouse tumor models. (5,6)

Suite 5, 20-30 Malcolm Road, Braeside VIC 3195, Australia. www.biologicaltherapies.com.au biol@biol.com.au +61 3 9587 3948

A randomized trial with 50 human subjects looked at the effect of concurrent vitamin C (five daily doses of 1 g each) and radiotherapy on different tumor types. More complete responses to radiation were noted in the vitamin C group at one month (87% to 55%) and four months (63% to 45%) post treatment. Side effects tended to be fewer in the ascorbate-treated subjects as well. Plasma levels of ascorbate in the treatment group were greater than control subjects, but less than the mean of 20 healthy subjects tested. (7)"

Lethal "targeted" radiation therapy vs. "stray" radiation plenty of vitamin C is a good idea before and after therapy to minimise side effects

The point of radiotherapy for cancer is to provide a lethal dose of radiation in a confined area, targeting the tumor. Of course cancer cells are very small and the border between tumor tissue and healthy tissue is microscopic. This means that inevitably radiation therapy will affect at least some healthy tissue surrounding the tumor tissue, and particularly if there are several areas of tumor in healthy tissue. The effects of this "stray" radiation depend on the dose that the healthy tissue gets. Most of the stray radiation is at a much lower dose that the lethal targeted radiation, particularly as it gets further away from the area targeted. This means that the radiation dose received by healthy tissue is largely sub-lethal; however it may still damage the cells due to free radical production and cause inflammation. *High tissue concentrations of vitamin C can "mop up" these radicals before they do damage, thus sparing the larger part of stray radiation affected tissue from damage*. To do this vitamin C needs to be in high concentration *during* the radiation therapy, which means that it needs to be administered *before* the therapy.

While vitamin C will also have this effect on the intensely irradiated tissue (the tumor), there is NO WAY that the small amount of vitamin C in the intensely irradiated tissue can stop the damage caused by such intense concentrations of free radicals. Radiation therapy provides an intense treatment to a small area, and any vitamin C in this area will be instantly converted to the ascorbyl free radical and/or dehydroascorbate. In this manner, the large concentration of free radicals produced suddenly by the intense radiation will rapidly use up any available vitamin C and for this reason it is not reasonably possible for vitamin C to interfere significantly with therapy at the point of application of the radiation.

Assuming the net effect of radiation therapy is to induce apoptosis in and consequent death of the tumor cells (this is what the research suggests), then the presence of vitamin C in this tissue after radiation therapy should not impair this process, once apoptosis is initiated in targeted cells. In fact, the presence of vitamin C may aid to control the extent of the inflammatory process that occurs in the area and limit escalation of the inflammation. The damage produced by the inflammatory process is caused by production of free radicals by immune system cells; vitamin C in sufficient concentrations may overcome this or help to limit it, thus reducing the severity of the inflammatory symptoms. Thus, vitamin C in sufficient concentrations may protect tissue surrounding the irradiated area from stray radiation, and aid in the control of the side effects produced by the radiation (8,9). In support of this idea there are studies that show that vitamin C *is* protective of side effects of radiation, to such an extent that the dose of radiation can be increased without making the side effects worse. A study by Blumenthal et al (on mice with tumors), published in the International Journal of Cancer, found that a combination of vitamin C and E permitted a large increase in the dose of radiation without worsening side effects, and that the vitamins did not compromise the therapeutic benefit of the radiation therapy (10). The vitamins also *treated* the side effects.

Summary

Vitamin C has not been shown in clinical studies to interfere with radiation therapy. The concern that vitamin C may interfere with radiation therapy is purely theoretical, but this concern is not supported by clinical outcomes.

Radiation therapy is generally limited to a dose that does not produce drastic side effects. These side effects occur due to stray radiation around the area of treatment, and also from direct radiation of the tumor tissue. Animal studies have shown that vitamin C administered with radiation therapy may allow the radiation dose to be increased without worsening side effects and without reducing the effectiveness of the treatment.

The emerging and probable sequence of how radiation therapy in combination with vitamin C affects cells goes as follows:

- Radiation produces free radicals that damage cell membranes (internal and external), cell components and DNA. The small amount of vitamin C in the intensely targeted tissue *cannot* protect this tissue from very intense radiation.
- After radiation produces *irreversible* damage to cells, particularly significant DNA damage, the damage leads to initiation of apoptosis mechanisms in the cell, leading to cell death (even though the radiation is no longer there).
- Cells which do not experience irreversible damage may be protected by vitamin C *if the vitamin C is in sufficient concentration*. Vitamin C reduces the side effects of therapy and may allow a higher dose of radiation to the tumor. This means that vitamin C needs to be present in high concentrations *before* the therapy so that it can be protective *during* the therapy.
- Cell debris is removed by phagocytes of the immune system. These phagocytes produce free radicals to digest dead cell debris, however this is an internal process within the phagocyte and is quite different to the radicals produced by radiation.
- Vitamin C may slow or help to control inflammation that occurs in the area *after* radiation, *if the vitamin C is in sufficient concentration*. .Vitamin C will not prevent tumor cell death if the cells have been “programmed for death by the radiation.

Suite 5, 20-30 Malcolm Road, Braeside VIC 3195, Australia. www.biologicaltherapies.com.au biol@biol.com.au +61 3 9587 3948

For further assistance with the nutritional therapies mentioned in this review, please contact the Biological Therapies team:

Biological Therapies

Delivering to the health community the highest European PIC/S Code of GMP

Suite 5, 20-30 Malcolm Road, Braeside VIC 3195, Australia

Call 1800 063 948 Toll Free within Australia • Phone: +61 3 9587 3948 • Email: biol@biol.com.au
Website: www.biologicaltherapies.com.au

References

1. Schmitt CA, Lowe SW. Apoptosis and therapy. J Pathol. 1999 Jan;187(1):127-37.

2. Lamson DW, Brignall MS.; Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Altern Med Rev. 1999 Oct;4(5):304-29.

3. Taper HS, Keyeux A, Roberfroid M. Potentiation of radiotherapy by nontoxic pretreatment with combined vitamins C and K3 in mice bearing solid transplantable tumor. Anticancer Res 1996;16:499-504.

4. Okunieff P. Interactions between ascorbic acid and the radiation of bone marrow, skin, and tumor. Am J Clin Nutr 1991;54:1281S-1283S.

5. Okunieff P, Suit HD. Toxicity, radiation sensitivity modification, and combined drug effects of ascorbic acid with misonidazole in vivo on FSall murine fibrosarcomas. J Natl Cancer Inst 1987;79:377-381.

6. Tewfik FA, Tewfik HH, Riley EF. The influence of ascorbic acid on the growth of solid tumors in mice and on tumor control by X-irradiation. Int J Vitam Nutr Res Suppl 1982;23:257-263.

7. Hanck AB. Vitamin C and cancer. Prog Clin Biol Res 1988;259:307-320.

8. el-Nahas SM, Mattar FE, Mohamed AA. Radioprotective effect of vitamins C and E. Mutat Res. 1993 Feb;301(2):143-7.

9. Garcia-Alejo Hernandez R, Martin de Miguel MJ, Seoane Leston JM, Romero Mendez MA, Esparza Gomez GC. [Radioprotective effect of ascorbic acid on oral structures in patients with cancer of the head and neck] Av Odontoestomatol. 1989 Sep;5(7):469-72.

10. Blumenthal RD, Lew W, Reising A, Soyne D, Osorio L, Ying Z, Goldenberg DM. Anti-oxidant vitamins reduce normal tissue toxicity induced by radioimmunotherapy. Int J Cancer. 2000 Apr 15;86(2):276-80.

Version ID: BioReview_Vitamin_C_and_Radiation_Therapy_20160920