The Concurrent Use of Antioxidants and Cytotoxic Cancer Treatments

A Speech to the 7th International Symposium for Biologically Closed Electric Circuits in Biomedicine[1]

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In early 2000 I published a small book on the topic of *Antioxidants Against Cancer* (Brooklyn, NY: Equinox Press, 2000). In this book I proposed that dietary antioxidants could be used to enhance the effectiveness of conventional cancer treatments, while decreasing many of their side effects.

Since that time, there has been an intense debate in scientific circles, as well as the media, over the advisability of such combinations. An increasing number of patients have turned to such complementary treatments. Many oncologists, meanwhile, have turned against antioxidants and warned their patients not to use them while undergoing conventional treatments. Claims have been made that such substances as vitamin C and vitamin E should be positively avoided. In fact, one researcher has suggested that cancer patients be entirely deprieved of all dietary antioxidants in an attempt to help kill their tumors.

This short talk cannot review the hundreds of scientific experiments that have been performed to test this question. However, I can give you a brief review of the scope of the controversy and provide a way for you to access the key articles and make up your own minds.

Labriola Vs. Livingston

In 1999, a debate flared up in the naturopathic field with two contrasting articles. First, Dan Labriola, ND, a well-known naturopath, published an article with oncologist R. Livingston, MD, that raised the possibility that antioxidants might interfere with chemotherapy [1]. The concerns raised were mainly of a theoretical nature: since some anticancer agents generate reactive oxygen species (ROS), antioxidants probably interfered with their activity.

This negative paper was then countered by another naturopath, Davis Lamson, ND. He reviewed the data and came to the conclusion that in practice antioxidants do not interfere with the action of cytotoxic treatments [2]. The article went over much the same ground that I had covered in my book and reached almost identical conclusions.

The Salganik Argument

Rudolph I. Salganik, MD, PhD, is a research professor at the University of North Carolina in Chapel Hill, who came to the USA from Russia in 1994. As one of his achievements, he created a strain of mice that inherited a tendency to produce an excess of reactive oxygen species (ROS). In 1999, he created a stir at the American Society for Cell Biology meeting when he claimed that depleting such mice of all dietary antioxidants increased the ROS activity in their tumors [3].

Dr. Salganik's claim was sensational, and the sensation was amplified by the ASCB and his university. A press release claimed that the "antioxidant-free diet had obvious health benefits for the mice. Their brain tumors measured about half the size of tumors in mice eating normal amounts of the vitamins. Their tumors also loooked better, with large areas free of malignant cells".

According to a follow-up paper in the journal Carcinogenesis, "increasing the ROS level might enhance apoptosis and thereby slow down tumor growth" [4]. Dr. Salganik's special mice were either given diets (a) depleted of antioxidants or else (b) antioxidant-enriched diets. There was dramatically increased apoptosis in the tumors of antioxidant-depleted mice.

However, "in clear contrast," he writes, "an antioxidant-rich diet had no impact on tumor growth." However, in their press release (Dec. 13, 1999), the University of North Carolina publicity department quotes him as saying: "Mice receiving extra vitamins A and E showed no benefit in either the size or incidence of brain tumors. They also had relatively short lives." It is not clear if he is saying that antioxidants decrease the life span of animals, since there was apparently no control group that received a normal diet.

In fact, he says: "In mice getting low levels of vitamins A and E, no negative effects were seen in normal cells, but about 19 percent of tumor cells showed evidence of apoptosis. In those ingesting normal quantities of antioxidant vitamins, only about 3 percent of tumor cells were apototic."

In the UNC press release, he drew broad inferences from this work. He claimed that "giving patients vitamins may prevent cancer cells from self-destructing and work against cancer therapy."

His colleague, Craig D. Albright, is quoted as saying: "These new studies raise important issues regarding the advisability of ingesting high levels of antioxidants as a potential anti-cancer benefit."

These are unwarranted extrapolations from the experimental data, since their published work does not involve the concurrent use of cytotoxic and antioxidant therapies at all. Although

1 Marienlyst Conference Centre, Helsingr, Denmark, July

Dr. Salganik and his colleagues called for "more research", the dramatic assertion of harm made headlines instantly all over the world, and led to a further decline in the public's faith in antioxidants, and trepidation on the part of cancer patients who were taking antioxidants.

In fact, Dr. Salganik has a clear therapeutic idea of his own: he would like to put cancer patients on a diet that is almost entirely depleted of antioxidants. He feels that the build up of ROS will be great enough, in this way, to render a therapeutic effect. (How he will avoid scurvy and other vitamin deficiency diseases is not clear.) I have found no references that this anti-anti-oxidant therapy has yet begun.

Oncologist Charles Simone, MD and I had the pleasure of debating Dr. Salganik at the June 2000 Comprehensive Cancer Care meeting in Arlington, VA. One can read an abridged version of this debate at the Center for Mind-Body Medicine website [5].

The Golde Statements

At around the same time, David Golde, MD, physician-in-chief at Memorial Sloan-Kettering Cancer Cancer, published a series of technical papers showing that vitamin C accumultes in some tumors cells. He used the occasion of these papers to extrapolate some conclusions concerning the concurrent use of antioxidants and chemotherapy. He told reporters that "Vitamin C might make cancer treatments less effective" (Science News 10/2/99).

Such arguments usually hinge on the fact that vitamin C can function in the testtube as a pro-oxidant. It is speculated that it might do harm to cancer patients, especially those taking chemotherapy. This is pure speculation. But similar scare stories have repeatedly appeared in the media.

What are we to make of all this?

The common denominator of most of these negative papers is some finding that has nothing to do with the concurrent use of antioxidants and cytotoxic drugs. But the researchers in question then express a fear that antioxidants will interfere with radiation or chemotherapy. If they express such misgivings in public their statements are amplified first by a news-hungry press office and then by the media itself. The result is another in a series of scare stories that reverberate around the world.

The first problem is that these fear statements do not flow or accord with the given facts. In fact, a sober review of the studies that have been performed over many decades shows that antioxidants enhance the activity of cytotoxics. I will give you a brief overview. (Shows slides from *Antioxidants Against Cancer*).

Almost, invariably, then, actually studies show that antioxidants enhance the effectiveness of conventional treatments. In other words, there is synergy. In addition, some of the serious side effects of radiation and chemotherapy are decreased. And antioxidants do this without the side effects of synthetic antioxidants.

Second, there is a good theoretical reason to believe that antioxidants in fact augment the work of conventional cytotoxics. It is an argument that was put forward by Kenneth A. Conklin, MD, PhD, an anesthesiologist at the University of California at Los Angeles (UCLA) [6].

Dr. Conklin explains the interaction between antioxidants and chemotherapy in terms of reactive oxygen species. ROS (which are sometimes loosely, but inaccurately identified with "free radicals") are:

1. Essential to life itself
2. Involved in cell signalling
3. Used by phagocytes for bacteriocidal activity
4. Produced by all respiring organisms as part of mitochondrial respiration

However, there is a negative side to ROS. They:

1. Cause oxidative stress due to drugs and environmental factors
2. Are involved in etiology and progression of many diseases
3. Are only held in check (or balance) by our antioxidant defense systems
4. Under conditions of stress (such as drugs) these antioxidant systems are exhausted.

ROS and Anticancer Agents

It is elementary biology that the normal cell cycle consists of:

- A pre-synthetic phase (G1 phase)
- DNA synthesis (S)
- Post-DNA synthesis (G2)
- Mitosis (M) during which G2 cells divides into two daughter cells

Each daughter cell may then reenter the division cycle (at G1) or may pass into a nonproliferative state (G0). As the length of the cell cycle increases, it is the duration of G1 that increases, while S, G2 and M remain constant.

While it may appear that we want to delay the entry of cancer cells into the cell cycle, this is NOT true for cells that are being subjected to cytotoxic treatment. In those cases, we WANT the cells to divide rapidly. The reason is that most anticancer agents cannot kill them unless they are rapidly and frequently dividing.

Conventional anticancer agents do the following:

- Block the synthesis of DNA precursors
- Damage the integrity of DNA
- Interfere with DNA replication
- Separate the two strands of DNA after replication
- Interfere with function of mitotic spindle

Cancer cells have "highly evolved" mechanisms to prevent lipid peroxidation. But excess ROS causes oxidative stress which results lipid peroxidation in cancer cells (as well as normal cells). This prolongs the G1 phase and may result in cells entering the dormant G0 phase. Thus, excess ROS ("free radicals") interfere with the cytotoxic effects of antineoplastic agents on cancer cells by interfering with a cancer cell's progression through its cell cycle. Tumor cells in G0

are unaffected by most chemotherapy and can usually reenter the division cycle after chemotherapy is completed. They can also repair damage done by drugs that do not require ongoing DNA synthesis (such as cisplatin).

Since anticancer drugs are effectively ONLY when cells are proliferating rapidly, it stands to reason that oxidative stress, which slows or arrests cell growth, interferes with the effectiveness of chemotherapy. It also explains why slow-growing tumors (such as lung or colon) are relatively unresponsive to chemotherapy.

Vitamin E is the main mechanism that cancer cells use to prevent lipid peroxidation. However, excessive oxidative stress may overcome even this highly evolved system, result in inhibition of cancer cell proliferation, and interfere with antineoplastic agents. ROS, contrary to being the mechanism by which anticancer agents kill cancer cells, prevent these agents from killing the cells.

The solution is to give the patient vitamin E, vitamin C and other selective antioxidants during chemotherapy. This will prevent the cancer cells from becoming dormant and thus expose them to the cytotoxic effects of the drugs.

Cancer itself causes oxidative stress. This has been experimentally demonstrated. In patients, oxidative stress is often compounded by poor nutrition. Tumor cells are usually able to overcome the oxidative stress of the condition and to proliferate rapidly. In fact, ROS damage to the host accelerate the promotion and progression of cancer.

However, administration of anticancer agents results in a much greater concentration of ROS than cancer itself. This high level of ROS during chemotherapy may overcome the antioxidant defenses of cancer cell. The result in that lipid peroxides reduce or halt cancer cell proliferation and thereby interfere with chemotherapeutic agents. Therefore, individuals with a relatively impaired antioxidant status are relatively unresponsive to chemotherapy.

On the contrary, supportive nutritional therapy with antioxidants during chemotherapy may overcome the growth-inhibiting effects of oxidative stress and maintain responsiveness to anti-neoplastic agents" (Conklin 2000).

Can dietary supplementation with antioxidants interfere with the mechanism whereby antineoplastic agents are cytotoxic to cancer cells? According to Conklin, "This is unlikely, since ROS are not involved in the mechanism of action of most anticancer drugs in current use." Bleomycin is an exception to the rule. However, although it is true that the scission of DNA by bleomycin does involved ROS, it also requires the presence of an electron donor. This is a function that can be fulfilled by certain antioxidants.

Conklin reviews the use of the following antioxidants and adds several dozen references that were new to me. (My own literature search turned up about 150 articles showing the benefit of concurrent use.) The nutrients he discusses, in a mainly positive fashion, are:

- Vitamin E
- Vitamin C
- Coenzyme Q10
- B-carotene
- GSH and glutathione esters
- NAC
- Glutamine
- Selenium
- Genistein and Daidzein
- Quercetin

According to Conklin, a test for whether or not a nutrient is interfering with chemotherapy is whether it decreases (a) myelosuppression and (b) alopecia. If it does, then there is reason to suppose that it is interfering with the anti-proliferative effects of chemotherapy. His major concerns are that certain substances called thiols, as well as selenium, may interfere with the activity of cisplatin. This is a caution I had also given in *Antioxidants Against Cancer*. In general, however, antioxidants may protect against heart or kidney damage or hearing loss, but not with the proliferative aspect of chemotherapy.

Cooklin's conclusion is that "dietary supplementation with antioxidants may provide a safe and effective means of enhancing the response to cancer chemotherapy." In particular, vitamin E "may prove to be an important nutrient for enhancing antineoplastic activity."

Conklin's article provides not just an excellent review of the data, but a cogent reason why antioxidants are in fact beneficial when used with conventional treatments. While we would all like a series of well-designed randomized controlled trials on this topic, it may be a while before we have that. However, we can reassure patients that the overwhelming mass of data accumulated so far supports the concurrent use of dietary antioxidants with chemotherapy.

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References

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