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CONCURRENT: Antioxidants with Radiation and Chemotherapy: Pros and Cons

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P R O C E E D I N G S:

DR. PRASAD: Thank you very much. It is my great pleasure to be here, but first I want to make a correction about my title. I have been listed both as an M.D. and a Ph.D. and I thought that I should have only one title. And therefore I just want to say I'm a Ph.D. rather than M.D. Nice to have the honor but I don't deserve one.

As he indicated, Bill, that this is a very challenging question, whether we should use antioxidant micronutrient in combination with radiation therapy and chemotherapy and I will try to show you some data.

First, before we do this you should know some statistics.

Just to impress on you, this is a major health issue. You know about 1.2 million new cases of cancer we detect every year. About 600,000 people die of this disease every year and among cancer survivors 10 to 12 percent of new cancer are induced by treatment modalities, as you know, X-radiation or chemotherapy, most of them are cancer-causing and in addition to that, of course, we are all aware that there are other late effect of a non-neoplastic nature such as aplastic anemia, a stunting of growth, mental retardation if the children are involved. So there are a lot of side effects among those who survive long-term. And the question is then how to reduce the risk of these types of side effects, not only in the case of acute side effect but also the long-term side effect of these treatment modalities.

But there are two opposing hypotheses, as you know, have been proposed. Either hypothesis that dietary multiple antioxidant micronutrient can be used as an adjunct to a standard or experimental therapy and this may improve the efficacy of treatment by increasing tumor response and decreasing the toxicity, this is the view that I support and I will propose or I will present to you data to support that hypothesis.

And the second hypothesis is opposing to that, namely antioxidants should not be used in combination with the standard or radiation therapy. If medical oncologists are not aware, right now 90 percent of medical oncologists or radiation oncologists believe in the second hypothesis but once they become aware of scientific fact then they switch to the first hypothesis and I will tell you why.

And some of the confusion in the literature had been because we are mixing, first, all antioxidant micronutrients in one group and if you divide the micronutrient in the two groups. One is a dietary antioxidant represented by ACE carotenoid and another is the antioxidants made in the body such as sulfhydryl compound like glutathione or its derivatives, cystamine, amifostine, and also the antioxidant enzyme, superoxide dismutase, catalase, glutathione peroxidase. And then you see how these tumor cells respond to these and how these two groups of antioxidant modified the effect of radiation and chemotherapy and based on the published result there should not be any argument and I will tell you why

if you look at the published data on these kind of two groups of antioxidant and, therefore, there should not be any controversy on that.

I want to say that, first, a few things you have to remember, that the experimental data show that tumor cells and normal cells respond differently to the same dose of individual antioxidants or multiple antioxidants. So they respond differently and therefore results of 10 on one cannot be applied to another one.

Another important issue is that not all antioxidants produce the same results on cancer cells in terms of qualitative effect or in quantitative effect. And the third thing that you have to remember, that at least on the cancer cell the effect of antioxidants is not related to the classical function of scavenging free radicals. So each antioxidant has much more complex effect on cancer cells than simply we say that these are all antioxidants. So those three points I wanted to mention it before I present my data.

And you can get an enormous amount of paper on this issue. There are rodent and human tumor tissue tested thus far have shown a varying degree of growth in and division differentiations and apoptosis *in vitro* as well as *in vivo* following the administration of high-dose individual or multiple antioxidants. When I say "high-dose" that means the dose which inhibits the growth of the cancer cell but do not affect the growth of the normal cell. That's the way we define "high-dose." And low-dose, of course, would be that dose which do not affect the growth of cancer cells and normal cells at all. And, of course, a toxic dose would be which kills everything. So for the therapeutic doses I will be using the word "high-dose" that imply that inhibits the growth of the cancer cells but not the normal cells.

Let me give you just a couple of examples of various effects. And this is melanoma cells and this has been treated with vitamin E succinate. You can see that is a highly malignant and they become differentiated. Differentiated means they become like a normal cell. They are making much more melanin. They have arranged themselves parallel to each other. That a molecule like vitamin E succinate can do all these kind of changes in the cell is amazing. And we found that this form of vitamin E is the most effective form of vitamin E from cancer growth point of view. Other forms of vitamin E do not have the same effect. Actually they are ineffective.

There have been always fights between the two large industries: Hoffmann-La Roche and Henkel (?) and for a long time I did not take sides. You know, I'm a poor professor. It is hard to fight in between two major nutrition industries. But when the data became apparent then I took a side.

We find that between the synthetic form and natural form of vitamin E and the natural form of vitamin E succinate appears to be more effective than the synthetic form, at least in the glioma tumor. In other tumors this may not be true.

This is another very interesting comparison. Here you have a different kind of vitamin E. You have melanoma cells and this is a human parotid carcinoma of the parotid gland. So ----- is a cancer of the parotid gland and here you have melanoma. And you can see that vitamin C, beta carotene ----- succinate, and the retinoic acid have a difference in effect. It depends upon the tumor type. In some tumor types vitamin C has a 50-percent growth inhibition; melanoma you have 95 percent growth inhibition. So one has to evaluate this kind of data that with different vitamins different tumor response will vary in a quantitative sense.

Another very interesting thing, this work done by Kimberly Klein (?) From Houston, that in the case of breast cancer the cells which were completely insensitive to hormone treatment after treatment with vitamin E succinate the same cells become very sensitive to hormones. I mean, this is a very exciting observation that a small molecule like vitamin E succinate can modify the breast cancers which are resistant to hormone treatment. Now they become more sensitive to hormone treatment. And this is, again, a very exciting observation regarding the function of vitamin E.

Then here we have compared a normal cell response to antioxidants and with a tumor cell. Here is a human fibroblast which are normal and here is the cervical carcinoma and this is ovarian carcinoma and the parameters that we have measured is the accumulation of mitotic cells in the mitotic phase which is an index of cell damage. And you can see that in both cancer cell lines vitamin E succinate has inhibited the growth but in the normal cell not inhibited the growth but decreased the level of mitotic accumulation but in a normal cell they have no effect, again showing that that cancer cell and normal cell to the same dose of vitamin E respond differently, and we have done in other parameters and they show similar results.

So again you have to keep this thing in mind that the normal cell and the tumor cell respond differently to vitamin E. I'll just give you the example of vitamin E because that's the vitamin I work on. But you can extrapolate that this is probably true because other people have done, with other antioxidants micronutrients as well.

Then how do these things work, so you have to do some mechanistic study and you have to use technology that we have available in molecular biology can measure the expression of genes like you can cook hamburger. It's very easy to do. It looks complex but it's very easy to do.

And you can see that the retinoid and carotenoid and vitamin E they will decrease the expression of these genes and the increase in expression of these genes are important for tumor cells to grow. So they inhibit it. Here they increase it because the increase in the enzyme and the gene expression are essential for continuation of the growth. So they increase it here because they will inhibit it if it is increased and if it is a reduced amount then cells will grow very faster.

In other words all these antioxidants down-regulate or alter the gene expression in a way that it will induce cell differentiation, growth in the region, and apoptosis to cancer cells but these changes do not occur in a normal cell because normal cell growths are not affected but in a cancer cell their growth are affected and you see enormous alteration of gene expression.

And that's why for cancer therapy it is important before you start your therapy radiation or chemotherapy damage the cell by this kind of mechanism and therefore when the cell receives additional radiation or chemotherapy it is already in the process of dying.

So supplementation, to supplementation normal cells and cancer cells respond differently but they also respond differently to deficiency. And in this case there was a deficiency. This work was published by a fellow in North Carolina that 90 percent deficiency of vitamin A and E can reduce the growth of the cancer cell without affecting the growth of the normal cell. So you can see that the cancer cell and normal cell respond differently to excess of vitamins as well as deficiency of vitamins.

Of course, this approach you will not do it because if you do it vitamin A deficiency can cause blindness. You won't be able to see it. Or vitamin E deficiency can cause all kinds of neurological disorders so you don't want to have a therapeutic approach of deficiency.

This is a human parotid carcinoma cells or ----- carcinoma cells. And here you can see where really a fact that at low doses of vitamin C tumor cell growth is stimulated and this is also true with the retinoic acid; this is also true for beta carotene. In other words if you give a single nutrient and it is possible that at low doses that can stimulate the growth of the cancer cell. And therefore we don't favor this idea of the cancer cell where you want to use a single nutrient; therefore, we are opposed to the idea of making a clinical trial with a single nutrient.

And therefore in addition to that individual antioxidants when they get oxidized act as free radicals. And therefore for these and many other reasons we don't favor the idea of using a single high-dose nutrient in any clinical trial.

And here is a mixture where you have seen that the dose of vitamin C by itself, all these four, has no effect. When you combine it, you have a 50-percent reduction in growth. And in this mixture if you increase the vitamin C doses you have an almost 90-percent reduction in growth. So this defines you that the concept that it is important to use a multiple vitamin is important.

And here I will show you this data that dietary antioxidants enhance the damage produced by radiation and chemotherapy where antioxidant will protect cancer cells against such damage and there has been a lot of study on this. For example, superoxide dismutase is an endogenously-made antioxidant and if you make cancer cells overexpress that they become very radio-resistant and so we don't recommend anything and same thing with the sulfhydryl compound. If you increase the sulfhydryl compound level in the cancer cell they will be protected against the radiation damage as well as against chemotherapy damage. So we don't recommend the endogenously-made antioxidant, at least in these two groups, for any treatment.

Here are some examples that you see that when you combine radiation with vitamin E succinate and there's a gamma radiation the combination is better than the individual agent alone. And if you can't see a protection against free radical in an individual system, in a cell culture, you are not going to see it *in vivo* because *in vitro* system is a clean system and the free radicals produced nobody's there to modify it.

Here is another very interesting example comparing radiation response to a normal fibroblast here and the cancer cell here. Radiation will damage both normal cells and cancer cells but when you add vitamin E succinate it does not get any mortified further in a normal cell but in a cancer cell it gets further reduced, showing again the idea that it is important that it is a selective effect on cancer cell enhancements of radiation damage.

This is the chromosomal damage. You see here, again, this is a normal cell, this is a tumor cell, and here it is interesting to see that radiation will increase. It's not a very good slide; I had to modify it because it doesn't show the differential effect. The point I want to make here, that in a control study you can see that in a normal cell vitamin E does not induce chromosomal damage but in a cancer cell vitamin E by itself increases the chromosomal damage. Radiation increases chromosomal damage in both normal cell and cancer cell but when you combine that in the cancer cell radiation damage is further enhanced in all three cancer cell lines but here you can see that radiation damage is decreased in the normal cell, again showing the selectivity of the modification of the vitamin.

Again, this is *in vivo* so when you are studying the cell culture here *in vivo* data showing an animal model that nobody survives if you give a single agent but 22 out of 24 and 20 they survived, almost cured the cancer in the animal model by combining radiation with vitamin E and beta carotene.

This is another example showing that vitamin C enhances the effect of 5-fluorouracil (5-FU). Here vitamin C by itself has no effect, 5-fluorouracil by itself has this much effect, but when you combine them you have a dramatic enhancement of effect of vitamin C. Same kind of thing you see with vincristine. Vitamin E enhances the effect of vincristine.

Here is another comparative study with a normal cell with albomycin. This is a Hela cell. It is a normal cell. You can see in the cancer cell you get a dramatic reduction when you combine with vitamin E, but in normal cells you don't get any further modification.

This is, again, an *in vivo* study done by some other fellow because I don't like to work with the animals so I let the other guy do it. So it's very interesting. It is a colon cancer transplanted in the animal and you can see this is a 5-FU alone and this is a vitamin E. Vitamin E's more effective than 5-FU and when you combination those you can see there is a dramatic reduction in the growth.

So what will we see in the future? I feel happy if somebody does an *in vivo*, although I wouldn't do it, but here is a combination: Tamoxifen, and you can see if you combine tamoxifen with a mixture of

vitamin C you get a better result than tamoxifen alone. The same thing is true with their other drug. In this case it's a DTIC, which is used in melanoma treatment.

My time is getting up so we have a critical point to reconsider in the clinical trial. You have to use daily administration 48 hours prior to a standard therapy, keep injecting throughout the experiment, and the reason this is effective because you have already established damage before you get chemotherapy and damage continues to progress because some of these antioxidants also prevent the repair of damage produced by radiation and they don't do so in the normal cells.

Here you want last clinical data, which is a ----- of nature and in the ----- you have seen much more up-to-date information that somebody else was going to present but from India could not come here. And so here is the very earliest stage of their study. You have a small number of patients here and you can see that there was one complete response when you have both combinations of chemotherapy and antioxidant and the partial response was two here, eight there, a stable disease one, three. You can see again some effect but I want to emphasize that this sample size is very small. But from these data and many other data you can see that these kinds of antioxidants do not interfere with the efficacy of a standard therapy.

Right now we don't have conclusive data to show about the efficacy issue but still the controversy is not about the efficacy. Controversy is about that it will reduce the effectiveness of conventional therapy. From all the data that we have seen it this doesn't seem to be the case experimentally in animal model now in a couple of clinical trials and, of course, in people who are doing alternative medicine they have done a lot of study, not well-controlled, well-designed, but from their experience if you take this information you will say it will ----- them to use the appropriate types of antioxidants at the appropriate doses as an adjunct to a standard therapy.

And, of course, the other issue that has already been emphasized in this meeting, namely lifestyle and diet, these are equally important, and I just presented one component, namely the supplement issue. Thank you.

(Applause)

QUESTION: Yes. Dr. Prasad, certainly it looks like your data suggests that it's potentially against the chemotherapy. A lot of people are taking these for prevention of disease and it certainly would not protect against the long-term effects because the normal effect --

DR. PRASAD: ----- the doses for the therapeutic is much higher than I recommend. So what we recommend that you carry on this and one month after completion of your standard therapy and then go back to a standard what we call inter-maintenance therapy and that will continue throughout his lifetime together with changes in the lifestyle and the diet. So these three are equally important complement in the management of cancer. Just taking supplement, you are correct, no, you don't stop with that. After you see better results you continue to have that at the reduced doses.

MODERATOR: Now for counterpoint, Dr. Labriola will give his thoughts on it and then that'll be followed by Michael Hawkins, who's sitting over there listening to it all, giving 5 or 10 minutes of commentary, and then we'll have some good time for a discussion, questions.

DR. LABRIOLA: Good morning. I'm Dan Labriola.

The answer to your first question, what is that, Wheel of Fortune, where they give you the answer and then you have to guess the question? Jeopardy. Well, I'm already dating myself here. The answer to the first question is yes, the question being aren't you the guy that wrote that paper on antioxidants, which has been asked in elevators, hallways, any place I've been since I've been here.

The answer to the second question is no, I do not deny antioxidants to my chemotherapy patients. On the contrary, every patient, every human being, needs to get a certain level of antioxidants all the time or you'll die. It's absolutely critical in order to maintain life, it's a matter of timing and that gives you the answer to the third question, which is dating. Timing is everything.

So what I'm going to try to do is there are a lot of extremes and one of the reasons I wrote the oncology paper and the paper, by the way, is in your reference and they did a really good job with the references here, by the way. I'm really impressed with that. Much of what's been written about the paper and has been written about the subject has been done by people who I think have only read the abstract and haven't really looked at the paper. So I really wanted you to have it as well as the letters to the editor so you have some real grounding about what's being said, what isn't being said, what's being suggested.

There are two extremes and I don't think you're going to find me at either extreme. There is the one that says you should use antioxidants all the time in any dosage you want regardless of chemotherapy, radiation, or other conventional therapy. I obviously don't agree with that.

The other extreme is that you should use no antioxidants and deny the patient antioxidants any time they're getting chemotherapy. I don't agree with that, either, and if you read the paper you'll find that it doesn't suggest that. But somewhere in the middle is what I'm going to be talking about and giving you some scientific background on today.

And that is under circumstances where a real possibility exists that antioxidants may reduce the efficacy of the chemotherapy those circumstances are where I say you err in the area of doing no harm and don't get in the way of the cytotoxicity of the drug.

Remember, I'm a naturopathic doctor. I'm the last guy in the world that's going to advertise chemotherapy and radiation. But the reality is that there are some circumstances where it works and if it's going to work I'm going to try to show you some real clinical ways to avoid potential interactions.

So my two objectives today are, number one, to give you some background and good clinical, scientific, and pharmaco- logical overview of the subject and, secondly, have you leave with some skills and some tools that if you choose to you can apply in your regular clinical practice.

I made some notes here. I have so many things I wanted to say I want to be sure I don't miss anything. I should point out that this is a relatively small capsulation of an 8- to 16-hour program that we teach for physicians and actually we've taught all over. The other thing I want to say is that this is a very small part of the big picture.

Antioxidants in chemotherapy are a relatively small part of what we do when we treat patients and I don't want this to end up looking like the end-all of what you do for treating cancer survivors. On the contrary, there are a whole lot of drug- nutrient interactions that are at least as important if not more important than this one with chemotherapy but the fact is this is the one I think that gets done, in our view, incorrectly the most.

Secondly, all the things that Dr. Prasad talked about, I mean, I really enjoyed Dr. Prasad's presentation. We spoke briefly on the phone before I came here and I was really hoping to dislike the guy so that we could not get along. And I see he wore his boxing shoes today, too. When he came in I thought uh-oh, this could be confrontational.

But I think he and I are really in very different areas of the spectrum in terms of the things that we're looking at, and I'm going to be talking a little more about clinical applications and I think Dr. Prasad was pretty clear. If he's not I will at least tell you my view is that unfortunately *in vitro* and animal studies do not reliably convert to human studies *in vivo*, which is too bad. I mean, if that were true we would have anti-angiogenesis drugs working every day and we would have solved most of the problem with treating cancer. It's a very difficult leap from animal and test tube studies to human studies, and I wish it wasn't but it is. So we have to be careful about how we interpret data.

So let's look at what we know about chemotherapy and radiation. Radiation and some chemotherapeutic agents achieve their cytotoxicity by creating reactive oxygen species. That's what ROS is. Those are free radicals, ions. They're charged particles, basically, and what those charged particles do is they attack living cells and they create basically DNA damage which in some cases will cause the cells to die. And we'll talk a little bit more about how that works.

The exact form of the free radical that actually achieves cytotoxicity, that actually does the DNA damage, is really very, very variable and not predictable. And the reason for that is something called the reactive oxygen species cascade. What happens, and I'm going to draw a little bit here.

The problem with being an egghead is that I often miss some of the practical stuff. I'm glad you all found that amusing.

You know, the original version of this paper was about three times as long as the one that published. I'm the first naturopath they'd ever published. And you've got to believe there's some mainline scientific. They were more than nervous. I mean, they were pretty open-minded but they came back with some comments like nobody is going to understand or care about the 17 pages of formulas and calculations and references that you put in here. You've got to make this more clinically relevant.

But I was originally trained as an engineer. I love math. I love doing this stuff. You know, there really is a pocket protector. You just can't see it.

(Laughter)

DR. LABRIOLA: So an ion is just any charged particle because a charged particle is going to do damage. And what happens is when these ions are running around in the body they come in contact with tissue. They come in contact with other molecules, whatever that other molecule is, and if they find a molecule of lower energy that's compatible they will exchange electrons. It's getting like dating again but in a different sort of way. This is not really clear. I'm sorry. It creates an ion of lower energy.

So the higher energy is going to exchange and do these things until it finally gets to homeostasis and everything in your body wants to get to homeostasis. It wants to level out. It doesn't like unbalanced things. So you have the search for homeostasis and in the process of these electron exchanges, and we could repeat this over and over and over, you're going to have a variety of different forms of free radicals.

And what's important about that, and I'm going to talk about that a little later, is that each of these free radicals is only quenchable by a certain class of antioxidants. I think Dr. Prasad alluded to that earlier.

So the form of the free radical that finally kills a tumor cell is not very predictable and this chain of events goes on, repeats and repeats and repeats and repeats, could end up with a large number of different kinds of free radicals before it gets to the DNA or the tumor cell at the right time during cell reproduction in order to cause that tumor cell to die. It's very similar to Phase I liver detoxification, actually. There's really a lot of similarities.

Okay, I am an egghead but I'll be quick here. So this is an alkylating agent. It's a form of chemotherapy where basically the drug adds an alkyl group to the end of human tissue and creates a proton which can result in another series of free radicals that eventually kill the tumor cell. These are very well studied. There's a lot of good references for that, just to prove to you that I wasn't an egghead.

So what do we know about these reactive oxygen species? Their cytotoxicity comes from discreet DNA damage. They don't come out and outright kill the cell. That's what was thought in the earlier days when these drugs were being developed. But it turns out that what the reactive oxygen species do is they create just enough DNA damage that when the cell goes into reproduction it looks at itself and says oh, my gosh, I've got this damage, and goes into apoptosis. In fact tumor cells are significantly more vulnerable to this kind of damage than normal cells so it just does itself.

The damage, as I said, is mostly during reproduction. The damage is usually otherwise sublethal, not only to tumor cells but to normal cells. That's an important concept. I mean, that's really why the drug can be used without killing the patient, hopefully.

Doxorubicin is adriamycin. I won't spend a lot of time on this but basically what it does is it has a little bit different molecular approach to reach the same conclusion and it basically oxidizes NADPH. It adds electrons to oxygen forming all minus compounds with oxygens and minuses. These are anion radicals and these anion radicals will eventually come in contact with tumor cells and do damage to the DNA in very specific places. That's all in the paper as well. They tried to take that out. I wouldn't let them take that out. It creates basically the same cytotoxicity in apoptosis.

So let's talk a little bit about systemic chemotherapy and what I'm really leading up to is the big picture of how these interactions occur. Micrometastases are these little tumor cells that get to a remote place and they're not located at the primary tumor. The concentration of the chemotherapy has everything to do with the number of micrometastases that are killed by the drug. This is, once again, very well studied; there are a lot of good references.

So, for example, if you're treating a breast cancer survivor, who perhaps had some positive nodes and you want to get as many micrometastases destroyed in order to prevent a recurrence at a distant place what you need is for those drug molecules to intersect with the micrometastases. Everybody with me so far? So you have these micrometastases out here. I don't know if they're round. Are they round, Dr. Prasad? Everybody's dodging my question here.

And you have these reactive oxygen species. I can't draw Pac-Man. I'm trying. Maybe I ought to do it this way.

I'm not going to draw too many of these because we don't have all morning.

So you have this basically chemical concentration of reactive oxygen species that were generated by the chemotherapy that are out hunting down these little micrometastases. But keep in mind the number of these reactive oxygen species and the concentration of them will determine how many micrometastases you get.

So you get one here, you get one here, get one here and in no circumstance, according to current pharmacology, do you kill them all with chemotherapy. It's one of the failings of chemotherapy is that you only get a certain amount and you're hoping that you retain enough immune function in order to get the rest.

But the number that you get has a significant effect on whether the patient is going to have a recurrence of the disease at a distant location. So that's how it works and I'm going to talk a little bit more about the quenching and the numbers here in just a moment.

Solid tumor response is very different and it's different in that when you increase or decrease the number of reactive oxygen species there is not a good way of assessing whether you've affected tumor response. And the reason for that is because tumor response is so variable. I mean, there have been a number of suggested clinical protocols to look at this and it's really difficult to look at because every patient has a little different response.

So basically what you're really looking at in terms of measurable data would be the 5-year and 10-year recurrence rate for patients who are at risk for distal metastases or disease from micrometastases. That would include also, by the way, lumpectomy patients -- we'll just talk about breast cancer for a moment -- who, say, have radiotherapy of varying efficacy because the reactive oxygen species may have been affected.

Everything making sense so far, fairly understandable? Good.

So what do we know about antioxidants? I'm frankly not going to disagree very much with Dr. Prasad. I said I was hoping to but I'm not going to do that. They quench reactive oxygen species selectively. I know we talked about that a little bit and I'll show you a few examples. Not every antioxidant quenches every free radical and that's an important concept. So that means that in some cases if you get really lucky and you give the right antioxidant during chemotherapy that uses reactive oxygen species you may not damage the reactive oxygen species that are out to kill the tumor cells but on another day you might and it's not very predictable. And because of the reactive oxygen species cascade that I talked about earlier, the various forms that occur along the pathway, you may not be able to predict that very well, so you may pick an intermediate one and stop the chain.

They quench reactive oxygen species generated by chemotherapy probably selectively. There are a number of studies that have demonstrated that but the very best one out there in my opinion was done in Finland by Erhola, Marina Erhola. I think it's reference number 23. And this is a point that's been argued by a lot of people and we've said oh, no, no, these reactive oxygen species are not quenched.

But what they did, what Erhola and company did, was they measured something called TRAP. And you can get this study, it's on MedLine and I have to read this. It's total peroxy radical trapping antioxidant parameters. So what that means in English is it's the total antioxidant activity in the patient in serum.

And what they did was they gave a number of small-cell lung cancer patients VAC. The Adriamycin is an anti-tumor antibiotic, this doxorubicin that I had up earlier. Cytosine is an alkylating agent, so I'm trying to keep these examples somewhat continuous. Vincristine is a plant-derived that probably is not affected very much by antioxidants in terms of being able to affect reactive oxygen species.

And what they determined was they were looking to see whether there really was an interaction between antioxidants in the body and the chemotherapy administered and what they discovered was that there was. And they would administer the drug and the TRAP would come down like that and then it would come back up. And for the first dose this was about 20 hours from administration. VAC is administered every 21 days. For the second dose it is one week.

Now, a lot of people draw a lot of conclusions, I think, that are beyond the life of this study, but the one conclusion from this study that we can draw that I think is very clear, and this is a human study, now, is that there is an interaction between the reactive oxygen species in the drug and the antioxidant level in the body.

Now, there's interesting stuff about this and that, as Dr. Prasad said, you need to maintain some baseline of antioxidant function or you die. So, anyway, in that context I think there is no question that my number two is correct.

Antioxidants can prevent damage to cells in the presence of reactive oxygen species probably selectively to cells in general. That's pretty well known. I don't think there's too much argument about that.

The other thing about antioxidants that's interesting is that you very possibly sensitize cells to cytotoxic agents with possibly greater effect under some circumstances. So the antioxidant question is not a black-and-white like it's good or it's bad. There are lots of things happening. We tend to simplify. We're all looking for the sound bite that answers the question. There is not a sound bite that answers the question here. It's going to be more complicated than that, and that's certainly the case here.

There are positives that make antioxidants useful and the more that we can find a way to use them in conjunction with conventional therapies without screwing up the conventional therapy the further down the road we're going to be.

I'm going to run out of time here in about five minutes. I had to put that up there but this is just two examples of how the quenching of free radicals is facilitated by antioxidants. Superoxide dismutase and catalase are two examples I chose. There are lots more. This is all, once again, pretty basic, very well-studied science.

I'm going to mention one other thing here and that is consider the source. It's interesting. This is a learning experience for me. I've always been very critical of conventional medicine in that drug companies have so much influence over what happens with what's published and oftentimes these relationships are not really laid on the table. I've learned since co-authoring this paper that we have much of the same problem in CAM therapy, which I found very, very discouraging.

Just to give you an idea of the kinds of sources that are out there, I just want to talk about these just very briefly. Oncology is a mainline, peer review, independent journal. I mean, they're pretty well known. They're very independent. They're very hard-nosed, I can attest to. They did a really good job. I mean, I was very impressed with them.

There are a number of new magazines and journals that are being published by companies whose products are actually being described at some level in the journal, and this is just one of a number of these. This is not a bad thing. I mean, they're really a good opportunity for individuals who want to publish who can't make it into the mainline journals. Many of them have a lot of good information, but it's unlikely that you're going to find any of these journals publishing anything that might affect their sales negatively. So you need to look and make certain that you understand what these relationships are because these relationships will affect what's on the printed page even though they're printed to look and feel an awful lot like a regular peer review journal.

Townsend Letters are really interesting. It's a forum and I really like Townsend Letter. It was started by medical physician in Port Townsend, Washington, Jonathan Collin, and it's an opportunity for anyone to literally say anything they want, and that's not a bad thing as long as you understand what it is. Most of the real advances that have come in medicine and health care have come from people who are outlanders who couldn't get into any mainland journal or get anywhere. So here's a chance to get this stuff on the radar screen.

But the other part of this is that some of the stuff that gets into these journals may not be that accurate and may not be that good. One interesting example is a fellow who wrote a letter actually criticizing the journal paper, the oncology paper, and stating that his experience for two years seeing every patient that went through the Fred Hutchinson Cancer Research Center determined without a doubt that there was no interaction between chemotherapy and antioxidants. So this is the Hutch but the thing that bothered me when I read this was the fact that I was the co-author of the Hutch's policy on supplement use during chemotherapy, which I thought was a big step for them. They used to say zero-zero. They actually came up with a protocol so I was surprised to see this.

And when I looked a little further I found out that the fellow's job there, you see, was a phlebotomist. In fact he was an assistant phlebotomist, used to draw blood, and had nothing to do with anything that would have determined that. But it made it on the printed page and a lot of people read it and it is, unfortunately, very confusing.

I just put my book up there. The whole point is any fool can write a book.

(Laughter)

DR. LABRIOLA: And just because it's in a book doesn't mean it's true or it's accurate.

So here are some clinical conclusions. Let's wrap that up. I think there's ample evidence that it's possible for antioxidants to reduce the concentration of reactive oxygen species and thus reduce the cytotoxicity of certain chemotherapies, not all of them, and they're described actually in the paper, and from radiation.

Antioxidants protect healthy tissue. This is a very important point. You cannot go without antioxidants. So the people that are on that other extreme I'm not going to agree with, either. So I'm in trouble with everybody right now but that's okay.

The other thing that I think is very important is that antioxidants have a lot of other possible effects. In my practice every patient gets a certain level of antioxidants. But what we've done is we actually have nutritional supplements manufactured where the antioxidant levels are adequate but they're low enough that they will not interfere with chemo and radiation and that was a struggle getting that done as well but that's where I am with the conclusions.

Clinical objectives are really interesting and when you're back in practice what I'm going to suggest to you is that you look at each patient individually. If you're going for the cure, if you have a Hodgkin's disease patient that's getting ABVD or MOPP and has a potential for a low enough stage that they're going to be cured, they're going to die of old age, would you risk using high-level antioxidants with that patient when many of the constituents of the most commonly used chemotherapies that are curative may actually cure the patient and you at least are introducing the possible risk of interfering with that cure? And I would say not only no but hell, no. I would never do that. This is my view but this is the way we practice. I think it's unwise to take that kind of risk.

But there are other circumstances where you might want to consider a different approach, and we've treated thousands of cancer survivors over the years. And one that really stands out to me was a supposedly end-stage ovarian carcinoma patient whose tumors actually responded well to carboplatin, carboplatin and taxol. But the patient couldn't tolerate the carboplatin/taxol. I mean, she absolutely couldn't. She'd rather die than have the drug.

So we sat down and we coordinated with all the oncologists that we work with and we came up with a plan where we used relatively high levels of antioxidants and other things as well. The taxol, which is not too sensitive to antioxidants, is actually sensitive to some other things, nutritional. And put together a plan to reduce the toxicity of the drugs and when we did that the patient was able to tolerate the carboplatin, got actually a reasonably good tumor response. They're still alive. They probably would not have been otherwise.

The last thing I'm going to say is look at the pharmacodynamics and pharmacokinetics. I won't spend a lot of time on that, it's in there, but I would say that treat effectively but avoid kinetic overlap. So if you want to do this the way I'm talking about doing it make certain that the life of the drug and the life of the nutritional supplements are not overlapping. That's relatively easy to do. You can still get the same benefit.

Adjust the kinetics for patient condition. Remember, these drugs are metabolized in the liver, they're excreted in the kidney for the most part, and when you have renal or hepatic insufficiency you have to adjust the numbers that are in the book. Remember, these are two- and three-compartment drugs. They're not only in serum, but they're in tissue, they may be in CSF, they may be in a number of other places. You need to pay attention to those issues.

Do no harm and, as I said before, there's a whole lot more than antioxidants and chemotherapy to providing good care. Everything from the organic things to what's going on up here has a whole lot of effect on what's going to happen in the rest of your body. So I hope you won't let this little corner of the treatment pattern distract you from the big picture.

So I'm sorry I ran a little bit over. Thank you very much.

(Applause)

QUESTION: The question was is there a list that people could look at to see when to and when not to use antioxidants?

DR. LABRIOLA: In your references in the oncology paper we've listed all of the drugs that are known to have reactive oxygen species components that could be affected by antioxidants.

QUESTION: Dr. Labriola, you commented on chemotherapy quite a bit. What about radiation? Is that in the paper as well?

DR. LABRIOLA: The paper didn't address radiation. The paper was specific to chemotherapy. Most of the same principles apply because the reactive oxygen species and the reactive oxygen species cascades function in essentially the same manner. There are some small differences but not that would affect you clinically except for the one thing, and it's beyond what we're going to be talking about today, I think, and that is looking at the basically the half-life of the radiation reactive oxygen species which is a little more complicated to determine.

MODERATOR: Thank you.

Dr. Hawkins.

DR. HAWKINS: Thank you. I want to say a couple of words just to emphasize some points that have already been made, I think, during the presentations.

I'm a traditionally trained medical oncologist and I have a medical oncology practice at the Washington Cancer Institute, where I'm the associate director. I'm also the medical director for the Smith Farm Center for the Healing Arts. And so I focus a lot on how patients not only in my practice but the patients that I see at Smith Farm approach these issues and some of the questions that they have.

And then finally I'm the chair of the Cancer Advisory Panel for the National Center for Complementary and Alternative Medicine where we're looking for promising data that can be then taken forward into larger-scale clinical trials to really show definitively the benefit of different approaches.

So when the issue of how we use antioxidants comes up I react to it in a number of different ways depending on which hat I happen to be wearing and I'm going to really try to integrate those responses for you here.

As a traditionally trained medical oncologist we are used to looking at data similar to this for chemotherapy treatment X versus chemotherapy treatment Y, for instance, or whatever the treatments happen to be where we plot time on the X axis and the percent of patients surviving on the Y axis. And this is standard treatment, protocol-driven treatment. All the patients on treatment X got treated the same way, all the patients on treatment Y got treated in a different but consistent way.

And what these types of randomized clinical trials do, these prospectively randomized trials so a patient agrees to go on either treatment X or Y not knowing which treatment they're going to get and frequently not having an overly large belief system in one treatment versus the other. The doctor says this is the treatment, this is the state of the art, this is what we're testing.

So this is by definition standard treatment. It's protocol-driven. It comes from outside in as opposed to healing, which is an individual process and is inner- driven.

What these types of trials do, though, is help to integrate all of the different effects of treatment Y and compare those to all the different effects of treatment X. In other words it takes into account the relative toxicities of the two drugs or the two treatments and the relative effectiveness of the two treatments against the cancer.

Patients say to me well, gee, isn't this alkylating agent likely to damage my immune system or cause immunosuppression? And the answer to that is yeah, it could do that but in some the effects of the alkylating agent, for instance, are greater against your cancer than any detrimental effects might occur from your immune system. So all of those various factors are taken into account.

And for many chemotherapy drugs we're not really sure exactly how they work. As time goes on, as the techniques get better and better, we start to learn more and more about them. But as was talked about earlier some of these compounds that we think are antioxidants may have most of their effects through mechanisms that aren't related to antioxidation at all, maybe effects on apoptosis or gene expression or whatever, so these kinds of trials would take all of that stuff into account and that's why it's important to do these types of studies.

Now, as was mentioned, *in vitro* data in animal models generate hypotheses for clinical testing, but they're not necessarily predictive of what's going to happen in the clinic. If it was that simple we would have cured cancer a long time ago because we know how to kill cells in a test tube and we know how to kill cancer cells in mice. So it's just simply not that easy. As I mentioned, there are multiple effects on the cells of antioxidants and we can't just look at a test tube experiment where you're looking only at the antioxidant properties because there could be lots of other things going on that you're just not measuring.

One thing that is very hard to mimic without doing the clinical trial is the effects on drug metabolism. So, for instance, if you're adding chemotherapy and, for instance, some panel of antioxidants, whatever, you don't really know until you do the study in man, in human beings, what the effect of those different compounds is going to be on the metabolism of the drugs, of the chemotherapy drugs. You're going to make it slow the metabolism, thereby increasing the dose effectively or increase the metabolism, thereby lowering the dose of the chemotherapy. You don't know that until you do the human studies. You can get hopefully some leads from your animal studies but you don't know for sure until you do the clinical trial.

There are also the effects of a compound like an antioxidant on the effects of the drug and this is what Dan was talking about. If you're going to modulate the antioxidant effects of a drug that kills via antioxidation that's a pharmacodynamic effect. You may not affect the drug levels of the Adriamycin, for instance, but you may affect what happens at the cellular level.

And finally frequently overlooked as one of the big reasons we do clinical trials is there is incredible patient variability. If you just look around this room you'll see how much variability there is in

the way human beings look. Well, that same variability goes on inside your body, and there's much more variability than there is in animal models where all the mice are genetically the same and all the cancer cells are identical in the test tube. And it's very hard to factor in that heterogeneity in any kind of preclinical studies.

One of the more sobering things in my time in doing drug development was the experience we had with interferon and interleukin-2. Both of these drugs have activity in renal cell carcinoma at a low level. Every laboratory, I think, in the world that looked at this found incredible synergy between interleukin-2 and interferon in an animal model and different labs looked at different animal models and they all found the same kind of thing. You gave tumor cells to the mouse through the tail vein and the tumors went into the lungs and then at a certain period of time you just counted the number of tumors that were in the lungs, sacrificed the animals and counted the tumors.

And in the animals that were untreated they had more than 250 metastases in their lungs. In the animals that got treated with interferon alone or interleukin-2 alone there was some reduction in the number of metastases but not striking and whether this would translate directly into any clinical benefit that you could detect is up to some question.

But when you combine the two there was a marked decrease in the number of lung metastases and this is the same experiment just done again and, again, the same kind of thing was seen, some effect with the interferon alone, some effect with interleukin-2 alone, marked anti-tumor effect with both drugs given together.

So we thought that this was going to be basically the end of kidney cancer as we know it once these two drugs could simply be given together in patients with kidney cancer, for instance. Unfortunately, while there may be some additive effect of the two drugs the synergy that is just so striking in animal models from lab to lab is not seen in the clinic and we don't really understand what that discrepancy is about, why there is so much discrepancy there, but the median time to tumor progression was the same, the response rates were fairly close, and there was a small difference in median survival. These were not randomized trials and so it's hard to say but clearly the striking synergy that we would have seen without even having to do the clinical or randomized comparison was just not there and if that striking synergy was present clinically we would have seen it.

So when we're talking about using antioxidants like we're talking about here in this forum these are drugs. Depending how you define the term we're using these compounds as drugs. We're using them to modify some behavior, either efficacy or toxicity, and so when you do this you absolutely have to look, do the clinical trials to detect unexpected interactions.

Clinically, again using some conventional treatments, Herceptin is a monoclonal antibody that has activity in breast cancer. It was combined with doxorubicin, the drug that we talked about earlier, which also has activity in breast cancer. What was seen was some improved anti-tumor activity but really a marked increase in the cardiotoxicity, the cardiac toxicity, of the doxorubicin. And this was really not well predicted from the preclinical studies that were done and might not have been picked up for some time had there not been a well done randomized trial. When it was combined with taxol that kind of enhancement was not seen and so clinically we use Herceptin now with the taxanes but not so much with doxorubicin.

Also the reason to do clinical trials is that some effects are only detectable when you have a relatively large sample size and an example of this is a drug called Zinecard, which does protect against the cardiotoxicity of Adriamycin, but there probably is some reduction in the anti-tumor effects. And so we found parameters clinically where this drug is useful and so we do use it in certain circumstances, but we don't use it in potentially curative regimens from the get-go.

So that's the view from somebody who sits on an advisory panel to NCCAM, the view from a medical oncologist. But what about from a patient's perspective? Patients need help interpreting these data. They are awash with data. They get data from the Internet, they get data from the bookstores, they get data from the evening news, they get data from Aunt Tillie, they get data from every well-meaning friend that they've ever had, and they need really help to interpret the data. There's a lot of confusion around the implications of preclinical data and that needs to be clarified for patients.

And there's a lot of confusion around claims from proponents and dire warnings from the opponents of different treatment. And a good example of this, again using a conventional medicine situation, is bone marrow transplantation, where there was a group of medical oncologists who thought in breast cancer that this was a great treatment and there were people over on this other side also trained in the same medical schools who felt that it was not yet proven. And it was very easy to find women who would go on bone marrow transplant; it was very easy to find women who wouldn't do it. It was very hard to find women who would say okay, flip a coin and I'll get randomized to one or the other.

But there were enough physicians who felt this was a really critical question and enough patients who realized that yes, they really needed to have this question answered that they were able to finally do the clinical trials and show that the bone marrow transplant really didn't add that much in women with advanced breast cancer.

That was a very critical study to do, okay? It's not dissimilar to some of the things we're faced with with CAM approaches, where there's a group that really wants to do it, a group that really doesn't want to do it. We have to find that middle ground.

So what do I tell patients? I tell patients that there's not as much clinical data as we would like, that the level of evidence that we have in this area is nowhere near what we have for the conventional treatments that we talked to them about and they need to understand the discrepancy in those data sets, that some risk exists using antioxidants in conjunction with chemotherapy and that risk is really very, very difficult to estimate in my opinion, and the risk is very considerable for potentially curative treatments, as Dan talked about in one of his last slides, and so I really warn patients about that and, quite honestly, most patients recognize that as a risk.

So those were the only thoughts that I had. I think now we have some time to open it up for questions.

(Applause)

QUESTION: My question is regarding the researchers who are currently performing protocols at major cancer institutes where there are conventional therapies being given. Is there a resistance on the part of the physicians or nonphysicians who are performing these protocols to add what we would consider complementary and alternative treatments into their protocols and if so why?

DR. HAWKINS: Well, from my perspective there's not. I think that the mainstream medical oncologists that I deal with are happy to have new treatments no matter what the source. And the problem is doing the trials in a well-controlled fashion so that at the end of the day we'll know whether to incorporate them.

Again, depending on the intervention you have to be careful about what patient population you use. You don't want to introduce something like this up front in a curative regimen but you might do it in a palliative setting. You see better effects there. Then you can say well, now we've got the clinical data to move it up. So it's tricky to find a good clinical situation where you're comfortable randomizing patients to get the treatment or not. But I don't think there's resistance at all to doing stuff in a well-organized fashion.

QUESTION: One of the things I appreciate from both of the presenters was this isn't a lump. It's a much more differentiated question, how antioxidants at different levels, different combinations, can be used. And it's clear from what you said is that there's probably going to be multiple types of clinical trials, different kinds of cancer, different kinds of radiotherapy, different types of chemotherapy. Is NCCAM fostering some of those clinical trials and if so what are they going to look like?

DR. HAWKINS: When you try to do work in this area it very quickly gets down to a very specific question that you're asking. And so what you need to do is take the data up to that point and say where does it make sense to ask that question and I think that there is a number of places that that question can be asked.

I think that probably some of the initial studies could be simply nonrandomized trials to make sure that the two treatments can be given tolerably together. But ultimately you're going to need to do a randomized study and I think that those studies initially would be done in patients who are by conventional standards not curable, advanced lung cancer, for instance, whatever, and if those studies are promising then move the treatments up to better-prognosis patients.

QUESTION: I'd like to add one thing. It's a really good question about the trials and when I spoke -- can everybody hear me on this? One thing that's important about all of the prospective trials that are being done with antioxidants and chemotherapy is the variability that's been discussed by a number of us in terms of the reactive oxygen species cascade and what you're interfering with. And the tendency has been in the past to have relatively narrow results and apply them over a broader area than at least I've been comfortable with and because we have -- if we'd find, for example, a positive study with Adriamycin, let's say, in Coenzyme Q-10 and that's not -- even though that's been suggested to be a positive for cardiotoxicity it has not been demonstrated to be safe in terms of its effect on the drug. If you find that in one study for one category of breast cancer patients it may not apply to other categories of breast cancer patients, for example, with different receptors levels or with different grade or other dissimilarities.

So when these studies are done I'm not certain that we're going to have enough to predict accurately the total result of what we're doing. So I think that's an important concept to keep in mind as these studies are being done.

DR. PRASAD: First, I completely support Dr. Hawkins' idea so I support that we have to have a well-controlled clinical trial to test the efficacy of various protocols and one of them are being tested which I developed in a setting where you combine conventional therapy, maybe as a Phase I trial or Phase II trial, has to be done before it is accepted in a mass scale. But, again, what we are hearing again from Dr. Hawkins or from my colleague Dan is fear, this implication, that again that sure, free radicals forget the tumor cell and the normal cells respond differently.

So the concept that we have developed about the role of antioxidant in terms of modifying the radiation injury you can write a small textbook on the radioprotective effect of an antioxidant like dietary antioxidant, endogenously made antioxidant, against radiation damage, and we see it very well established. And you can write it, but we cannot apply that principle to cancer cells where the data are not showing this is the case. This is my problem with the opponents of this case that they tend to apply.

First they mix all the antioxidants together, endogenously and dietary, and then on top of that they try to extrapolate what is observed in a normal cell to a cancer cell but none of the data show that this can be done.

And so suppose if you expose the cancer cell for five minutes with a small dose of antioxidant. It is possible it could work as a regular protective agent. I mean, it's possible so I'd like to make this caution that you cannot extrapolate the data from one experimental system to another. And in defense of the animal model the reason we can't have some of those that Dr. Hawkins mentioned about studies and

other studies was done with ----- . This is a sulfhydryl compound and the animal studies showed that it protects only normal cell against radiation damage, not the cancer cell. So in the animal model in the tissue culture model it was very exciting for people who discovered it.

But when it went to a human trial it caused bone marrow hypoxia, it caused hypertension, and all kinds of side effects. So this is not the fault of the animal but humans are very sensitive to the same drug. So many times in humans we cannot achieve the efficacy of the drug that we need to, but in case of antioxidants toxicity is not the issue and therefore, again, we have to consider antioxidants as a different group even though at high doses and I completely agree they could be considering it a drug because it has some action other than as given in free radicals.

QUESTION: Two years ago at a similar gathering, just to make a long story short, the consensus of the panel at that time was those who want to use antioxidants in their protocols should not use antioxidants the day of chemotherapy or within eight hours of radiation. Now I'm hearing you shouldn't use it for two to three days after chemotherapy and radiation. I agree with Dr. Prasad the fact that you have all these confounding factors. Particularly we're telling all our patients we want you to eat lots of vegetables, fruits, the cruciferous vegetables which are rich in glucosinolates et cetera, et cetera. So you've got a -- even in some of these trials that you're doing are going to be confounded by all other factors. How do you address that?

DR. LABRIOLA: Well, let's start with the first one. The eight hours, one day, I'm not sure where that came from but it doesn't have anything to do with pharmacology. The fact is that we can predict the life and activity of most of these drugs not only in serum but also in tissue. So you have drugs like the pyrimidine analogs that you can probably wait only 8 hours, things like 5-FU, although that's not an antioxidant. It's sensitive to other things. You have other drugs, like cisplatin, where the drug is active for months.

So to make these kinds of generalities, I mean, I don't know who was on the panel or what they were saying but they probably needed to go back and look at the pharmacokinetics of the drug. Also, you need to look at the pharmacokinetics of what you're taking. If you're taking vitamin E, for example, fat-soluble vitamins have a longer half-life than the water-soluble vitamins. And I don't want to drag this too far but it depends on the specifics. I think that's what's really most important.

And the other thing is we're looking at a very isolated part of the treatment picture, and I hope I had made that clear. Antioxidants in chemotherapy are not the only determining factor about what you should do and what you shouldn't do but should contribute to your clinical judgment of what you're going to do with the whole patient and I think Dr. Hawkins made some really good points about -- and I think I made a few as well on whether you're talking about curative or palliative patient and it's a matter of degree.

Hopefully, that answers.

Dr. Prasad.

DR. PRASAD: The timing is very important and the reason we suggest 48 hours is high dose multiple antioxidant dietary work not endogenously made because it has been shown in humans that retinoic acid, vitamin C at high doses in some tumors does help by itself inhibit the growth of the cancer 20 percent, 10 percent, 30 percent. It does. It does have an anti-cancer property when you use it in high doses in humans.

And so what we do, we suggest that you use these high doses so that the damages which are initiated in new tumor cells eventually, like apoptosis or any other kind of death, have already initiated. Now you come with the chemotherapy and radiation. The cell is not only suffering damage after radiation damage. Only two-thirds of radiation is by free radicals and there they're not acting as antioxidant

modifying the effect of free radical, but radiation also causes damage by ionization. One-third of the damage is caused by ionization.

So now these cells have a further damage. Again, like Dr. Hawkins said, this is the hypothesis. It has to be tested in human clinical trials. But I'm saying the sequence of mechanistic that the laboratory data suggest.

Now, it has been shown that the antioxidant will inhibit the repair of potentially lethal damage produced by radiation, and this is work by Dr. John Little (?) or Harvard, a very elegant study published, and so now you think that cancer cell is not only further damaged. Now it cannot repair the damage of potential lethal damage caused by these agents and therefore you see continuously doctors ---- you start giving every day even one month after the completion of radiation therapy and therefore you will see the enhancement on a cancer cell and since these ----- don't occur in the normal cell you will see the damage to the normal cell only by radiation or chemotherapy, whatever damage it caused.

In certain cases this may protect. In other cases antioxidants may not protect as much normal cell on certain criteria. So the timing is extremely important. You can start after radiation therapy or just before radiation therapy.

QUESTION: Okay. Building on some of the things that I've heard or, Dr. Labriola, you mentioned carboplatin and taxol where you did feel in that one case it was fine to give some antioxidants. You also just mentioned cisplatin and that may have activity for months. Dr. Prasad mentioned amifostine, which has been approved and gone through the trials in the context of ovarian cancer, with cisplatin and taxol as a fine, fine combination to not impact efficacy and maybe reduce the side effects of the chemo. When you put it all together it's a little confusing on the one hand to talk about a safe window of cisplatin, yet here's a synthetic powerful antioxidant, amifostine, which has been tested fine with the chemo drugs and would you not take that ----- and say it's probably okay at least with cisplatin and taxol in the context of ovarian cancer that if amifostine as an antioxidant has proven to be all right would not other antioxidants be all right?

DR. LABRIOLA: Well, that's a really excellent question. I think it comes down to a couple of things. The example of the carboplatin or cisplatin was not the drug but the patient circumstance. Everything that you mentioned in the way of antioxidants reduces or at least we believe reduces the efficacy of the drug. In some circumstances clinically my suggestion is that it's okay to reduce the efficacy of the drug if the other benefits warrant it.

So, for example, you have a patient that you know you're not going to cure, but you know you can have some short- to moderate-term benefit by being able to use the drug. If they're going to get good tumor response you can probably endure some reduced activity on the drug in order to reduce the side effects so the patient can do it. So the carboplatin-taxol example was the patient couldn't tolerate any of that, probably would have died very quickly. She was in fact able to tolerate some carboplatin, is actually still alive, but it didn't certainly cure her disease as compared to the Hodgkin's disease example where if you know you've got a cure right here, you've got the bird in the hand, why would you take a chance on a potential interaction?

The thing about the antioxidants is that antioxidants are all very individual. Amifostine, I think there are still some questions as to how much it reduces. It does reduce the efficacy but in most cases not enough.

There are other drugs, like Mesna, which is actually a wonderful example. This is an antioxidant that metabolizes so quickly into the urinary tract that it doesn't have much of any effect anywhere else in the body and it's used with drugs, like ifosfamide and some other alkylating agents to prevent all the urinary tract damage that makes those drugs very difficult to use otherwise.

So here you have a very powerful antioxidant. You take the antioxidant. You get injected with the antioxidant. It goes straight through your urinary tract, protects the urinary tract against any kind of literally cell damage from the alkylating agent, but it doesn't protect any of the rest of the body to enough of an extent to have an effect. So each one of these is individual.

One of the mistakes I think that gets made is people generalize the activity of antioxidants. I think that's a mistake. The other thing is generalizing whether they're ever a good idea and I think what Dr. Prasad said I would agree with. We spend a lot of our lives for ourselves and for other physicians calculating out what we call a protected zone -- it's in the book if you want to read my book -- with the area where the drug may be vulnerable and making certain that we don't use a lot of antioxidants and other nutritionals that could interfere during that period.

But outside of that period, I mean, you can argue for and against but most of the evidence in my view is positive for the use of higher dose antioxidants. I'm not a huge megadoser but in those areas where you know you're not going to keep the drug from doing what you want it to do why not?

It's a benefit-risk ratio. I have this conversation with every patient. If the potential benefits outweigh the potential risks and you really understand what those both are, go for it. And that changes when you're inside or outside of that protected zone.

(Whereupon, the PROCEEDINGS were adjourned.)

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