Vitamin E, Pentoxifylline, and Radiation Fibrosis

Radiation therapy is often a component of care for patients with cancer. While radiation has great capability to kill cancer, side effects are possible. Fortunately, dramatic strides have been made in improving radiation treatment over the last few decades – modern computing and technology allow focused delivery of high radiation doses to tumors with four dimensional image guidance, dramatically limiting radiation dose to normal, healthy structures in the body. (For those of you wondering – the “fourth dimension” is that of time – for example, localizing a tumor in three dimensions, but also tracking through space as it moves over time.)

However, the risk for side effects to normal tissue remains, even when limited by the most sophisticated radiation technology. One common late or long term side effect following radiation therapy is “radiation fibrosis.” The term fibrosis describes a process of scarring which can develop in the soft tissues of the body, such as skin, muscle, healthy lung, or breast tissue. Radiation fibrosis refers to a transformation from soft, supple, and pliable soft tissue to one that is more stiff, less flexible, and less able to normally withstand and repair after other minor injuries.

On the cellular level, radiation induced fibrosis has been linked to abnormal fibroblast activity. Fibroblasts are a class of immune type cells which normally help tissues repair after injury. However, in situations of radiation induced fibrosis, these cells overreact, and produce excessive extracellular matrix around healthy cells. This process is triggered by a free radicals incited by therapeutic ionizing radiation.

In cases of radiation induced fibrosis, the initial inflammation triggered by therapeutic ionizing radiation spirals out of control, and in the irradiated area, the inflammatory response turns chronic, with potentially significant resultant scarring.

What can be done? Radiation damage acts through a free radical mechanism, and radiation scarring can often affect small blood vessels and result in decreased blood flow to irradiated tissue. Due to these mechanistic underpinnings, a group in France has published some work on combination therapy with Vitamin E (an anti-oxidant, or free radical scavenger) and pentoxifylline (a vasodilator, marketed as “Trental”). Together, these medications seemingly could target part of the mechanism (oxidative damage) and part of the complication (reduced blood flow).

The French group published a study in 2003 in the Journal of Clinical Oncology that examined the potential benefit to six months of treatment with a combination of Vitamin E and a vasodilating drug by the name of pentoxifylline. In this study, 24 women with a history of breast cancer and radiation induced fibrosis of the skin and underlying tissues were randomly assigned to one of four treatment groups: 1) Vitamin E alone, 2) pentoxifylline alone, 3) combination therapy with Vitamin E and pentoxifylline, and 4) placebo. The investigators reported that radiation induced fibrosis surface regression was significantly improved among women taking the combination of Vitamin E and pentoxifylline, such that the mean radiation induced fibrosis surface regression was reduced in comparison to placebo in 60% vs. 43% of
patients. The “p-value” for the comparative statistic was $p=0.038$ (for the non-statistician readers, that $p$-value suggests that the findings had only a $4$ in $100$ probability of being due to chance).

While many physicians employ vitamin E and pentoxifylline in cases of radiation fibrosis based on this data, I remain highly skeptical of its benefit. First, it is shocking to me that in this study, there was a $43\%$ improvement among patients taking placebo! That is an extraordinary placebo effect! Rarely in any study of medication are the benefits so great – and in this study, it appears that the majority of the benefit was realized by those taking nothing! Second, as one carefully examines the data, it is clear that the patients taking placebo had the same benefit, or even a slightly increased benefit, compared with those patients that were taking Vitamin E only, or pentoxifylline only. Thus, if the benefit of the combination drug therapy is real, there is a yet to be established synergistic phenomenon upon which the therapeutic benefit completely relies. It is surprising to me that each drug alone yielded no benefit whatsoever over placebo.

While it makes some sense that these medications are directed at helping some of the problems in radiation induced fibrosis, I am not convinced of their benefit. As well, in this study, the outcome measured was soft tissue fibrosis among patients treated for breast cancer. I know of no comparable data among patients treated for other cancers or for fibrosis of other body sites or organs.

In my practice, I will offer to patients with radiation fibrosis a trial of therapy with Vitamin E and pentoxifylline, given that they are very safe medications, though I upfront explain my uncertainty that they will be of benefit.

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