LE Magazine July 2002

REPORT

Theanine Enhances Chemotherapy And Reduces Side Effects

Cancer cells are good at getting rid of drugs designed to kill them. They use tiny pumps to expel what they don't like-such as doxorubicin (adriamycin), a drug used for chemotherapy.

For several years, researchers in Japan have been investigating the potential of an amino acid from tea to enhance the ability of doxorubicin to work. Known as theanine, this unique dietary supplement has already proved valuable in other areas of health. Early studies showed that if theanine is added to a regimen of doxorubicin, tumor weight could be halved compared to the effects of the drug alone. The experiments were repeatedly done, and every time theanine enhanced the killing capacity of doxorubicin. Researchers soon discovered why.

Theanine increases the amount of drug getting into tumors. What's exciting, though, is that while it increases the level of "dox" entering cancer cells, it doesn't increase those levels in healthy tissue. That means that theanine selectively enhances toxicity only where it's needed. This makes theanine different from the drugs presently being used to overcome "multi-drug resistance".

Those drugs work by suppressing a protein that enables cancer cells to resist chemotherapy. The problem is that the multi-resistance drugs suppress the protein all over the body, which causes toxicity. Theanine doesn't do this. Instead of suppressing a protein, theanine pretends to go along with the program, enters cells and then throws a monkey wrench in the works. The original studies showing these effects were published in Cancer Letters and Toxicology Letters.

Theanine protects healthy cells

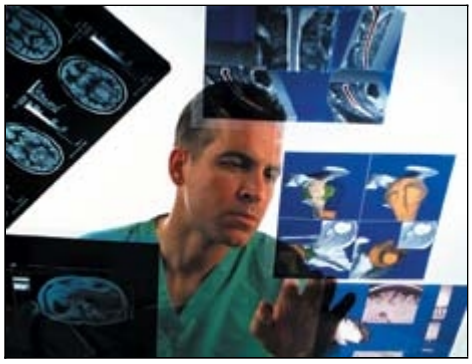
Besides enhancing doxorubicin's cancer-killing effects without harming healthy tissue, theanine also keeps doxorubicin out of healthy tissue. This is a major added benefit since one of the drawbacks of doxorubicin is its toxicity to the heart.

Dox-induced cardiac toxicity is associated with high levels of lipid peroxidation-free radicals. A study published in 1996 shows that theanine reverses lipid peroxidation in cardiac tissue which doxorubicin causes to double. In studies on rodents, complete reversal of lipid peroxidation was achieved with 100 mg/kg of theanine. One of the supplement's actions is to reverse the loss of glutathione peroxidase, an enzyme that is depleted by the extra free radicals.

Doxorubicin suppresses the ability of cancer to spread. When combined with theanine, it works even better. The same researchers conducted a study on the suppression of liver metastases in mice with ovarian sarcoma. Metastases were fewer than with dox alone.

Theanine makes chemotherapy work

In 1999, researchers did a study testing theanine in conjunction with a drug similar to doxorubicin known as idarubicin. Idarubicin has been tried against drug-resistant leukemia cells, but it causes toxic bone marrow suppression and can't be used.



Researchers wanted to see if theanine would make the drug work. In the first experiment, about one-quarter of the standard dose of idarubicin was used. At this dose, the drug doesn't usually work, and doesn't cause toxicity. When combined with theanine, however, idarubicin worked-without toxicity. Tumor weight was reduced by 49%, and the amount of drug in the tumors doubled. In the next experiment, theanine was added to the usual therapeutic dose. Theanine increased the effectiveness of the drug, and significantly lessened the usual bone marrow suppression. Leukocyte loss was reduced from 57% to 37%.

How does it work?

Glutamate is a multi-faceted amino acid. One of its jobs is to help create glutathione, an important detoxifier. Glutathione is the liver's first-line defense against drugs and chemicals. It is also one of the things cancer cells use against drugs and chemicals. Cancer cells use glutathione to detoxify doxorubicin and escort the drug out of cells. Theanine works because it interferes with the process.

Theanine is an amino acid which is structurally similar to glutamate. This is the key to its success. It is able to fool cancer cells into letting it in, but once inside this Trojan horse acts very differently. Glutamatic acid, or glutamate, is one of the components of glutathione, the drug detoxifier. Because it looks like glutamic acid, cancer cells take up and mistakenly use the theanine to create glutathione. But the glutathione they create with theanine does not detoxify like natural glutathione. Instead, this theanine-based glutathione appears
to block the ability of cancer cells to detoxify.

Researchers working with ovarian cancer have discovered that theanine lowers the amount of glutathione in cancer cells. Without this raw material, cancer cells can't run their detoxification system. They lose their ability to detoxify, and thus, doxorubicin becomes more toxic to them. Up to twice as much doxorubicin stays in cancer cells treated with theanine.

These findings on glutamate and this detoxification system in cancer cells is very important because most research on drug resistance in cancer cells has been focused on a different system altogether. By showing that a non-toxic, readily available dietary supplement can enhance the amount of a chemotherapeutic drug that gets into cancer cells, and at the same time reduce it in healthy cells, Japanese researchers have made a great leap forward. Theanine may be an ideal partner for doxorubicin chemotherapy.

Note: The human equivalent dose of theanine as a chemotherapy adjuvant with doxorubicin is 500 to 1,000 mg/day. Be aware that no human studies have been conducted.

References

Sadzuka Y, et al. 1996. The effects of theanine, as a novel biochemical modulator, on the antitumor activity of adriamycin. Cancer Lett 105:203-209.

Sadzuka Y, et al. 2000. Improvement of idarubicin induced antitumor activity and bone marrow suppression by theanine, a component of tea. Cancer Lett 158:119-24.

Sadzuka Y, et al. 2001. Enhancement of the activity of doxorubicin by inhibition of glutamate transporter. Toxicology Lett 123:159-67.

Sadzuka Y, et al. Efficacies of tea components on doxorubicin induced antitumor activity and reversal of multidrug resistance. Toxicology Lett 114:155-62.

Sugiyama T, et al. 1998. Enhancing effects of green tea components on the antitumor activity of adriamycin against M5076 ovarian sarcoma. Cancer Lett 133:19-26.

Sugiyama T, et al. 1999. Combination of theanine with doxorubicin inhibits hepatic metastasis of M5076 ovarian sarcoma. Clin Cancer Res 5:413-16.

Back to the Magazine Forum