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Cancer Care

# Immune Enhancement, Avoidance of Interactions Are Keys to Chemotherapy Support

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It is no secret that many people with cancer take nutraceuticals and botanical medicines in conjunction with conventional chemotherapy, in the hope of enhancing the therapeutic effect, minimizing side effects, and improving their odds of a long, relatively healthy life.

The impulses are certainly understandable, but the mixing of supplements and other natural products with anti-cancer pharmaceuticals raises concern about the potential for supplement-drug interactions.

Until recently, there's been a void of good science about the ways in which commonly used supplements interact with common chemotherapeutic drugs. With the emergence of integrative oncology emerges as a clinical discipline, researchers have begun to turn serious attention to this issue.

There are essentially two types of interactions: those in which one substance speeds the metabolism and clearance of another, thus decreasing the latter's efficacy; and those in which one substance inhibits the clearance of another, making it toxic. It all comes down to how various drugs, nutrients, and botanical compounds are processed by the liver.

Roughly 75% of all known drugs are metabolized through the cytochrome P450 class of enzymes, making this a key locus for research on interactions.

### *Filling a Data Void*

Researchers at MD Anderson Cancer Center, Houston, are engaged in a wide-ranging pharmacologic assessment of roughly 30 commonly used natural products, and their potential for interaction with common chemo drugs. This line of work will be important for guiding clinical care of people with cancer.

"When they don't have any data, oncologists tend to tell patients not to risk it with natural products," said Judith A. Smith, Pharm, D, Director of Pharmacology Research at MD Anderson's Department of Gynecologic Oncology. This may be prudent, but it can result in patients missing out on the benefits that some natural products might confer.

Though work in this field is still at an early stage, Dr. Smith told Holistic Primary Care that her team has already identified a couple of nutraceuticals & natural products that pose little risk of interaction. They've also hit on one that should definitely be avoided.

Her group recently published a paper in the Journal of the Society for Integrative Oncology, on the interaction potential of AHCC (active hexose correlated compound), an extract obtained from a hybridization of several species of medicinal mushrooms. AHCC is supported as a cancer care adjunct by over 25 studies, and has been shown to decrease side effects of chemotherapy — including hair loss and bone marrow suppression.

In Japan, where AHCC was developed, it is often used in conventional practice, and it has attracted the interest of several prominent American oncologists.

### *AHCC: Little Risk of Interaction*

Dr. Smith's team conducted two studies: an in vitro metabolism study, to determine whether AHCC can inhibit P-450 detox pathways (i.e. if it might increase a drug's toxicity), and an ex vivo human liver cell induction study, to evaluate whether it induces P-450 activity (i.e. if might reduce a drug's efficacy).

The in vitro work indicates that AHCC does not inhibit the major P450 detoxification pathways, meaning it will not delay breakdown of most chemo drugs. "AHCC is unlikely to result in increased toxicity when used in combination with chemotherapy or supportive therapies such as anti-nausea medications or antidepressants."

The ex vivo study indicated that AHCC does increase CYP450 2D6 activity. Therefore, it may have the potential to modulate the effect of drugs metabolized through that pathway. Fortunately, this is not a predominant pathway for metabolism of commonly used chemo agents, with the exception of doxorubicin and tamoxifen.

Tamoxifen must be metabolized by the 26D pathway to be converted to its active form, so induction of 26D might increase the effect of the drug. There are some case studies suggesting this does occur, though the interaction is not

well understood. It is also possible that AHCC's induction of 26D would increase tamoxifen toxicity, though this has not been observed. Until more is known, it is wise to be cautious in combining AHCC with tamoxifen. But since most other chemo drugs are not metabolized via 26D, there is little risk of interactions.

Among the other compounds Dr. Smith's group has studied, L-glutamine is the only other so far that shares AHCC's low potential for interactions. Some clinicians—and many cancer patients—believe L-glutamine supplementation bolsters immune function and diminishes mucosal injury from radiotherapy.

Noni juice, popular among cancer patients and promoted for immune strengthening, is a must-to-avoid with chemotherapy, said Dr. Smith. The foul-smelling, anthraquinone-rich juice from this Polynesian fruit is a powerful inducer of CYP450 enzymes.

### *Reducing Toxicity, Improving Lives*

Lise Alschuler, ND, FABNO, an integrative oncologist in Bedford, NH, said it is important to understand and to respect the motives that drive cancer patients to augment allopathic cancer treatments with natural products.

"The prospect of having cancer invokes fear of pain, suffering and death. The treatments are, for many, as terrifying as the disease itself. Chemotherapy, the mainstay of conventional treatment, is perhaps the most feared of all. Nausea, diarrhea and/or constipation, mouth sores, fatigue, numbness and tingling of the extremities are common and sometimes severe. The need for additional therapies that will reduce the toxicity of chemotherapy is great."

Dr. Alschuler, is co-author, with Karolyn Gazella, of The Definitive Guide to Cancer: An Integrated Approach to Prevention, Treatment, and Healing, now in it's 3rd edition. Herself a breast cancer survivor--or "thriver" as she prefers it—Dr. Alschuler is particularly enthusiastic about AHCC's potential.

"What makes it so exciting is its ability to improve both duration and quality of life. Two studies of patients with highly incurable primary liver cancer have shown that the individuals given AHCC experienced a significant prolongation of life as well as dramatic improvement in their quality of life."

In these trials, AHCC reduced side effects while enhancing the tumor killing, translating into higher quality of life and increased survival times (Cowawintaweewat S, et al. Asian Pacific J Allergy Immunology. 2006;24:33-45. Gao Y, et al. Cancer Immunol Immunother. 2006; 55:1258-1266).

### *AHCC & the Immune System*

One reason cancer cells are so dangerous is that they directly suppress immune function. Specifically, they suppress dendritic cells, the roving "eyes" of the immune system. Normally, when these cells encounter a cancerous or otherwise aberrant cell, they send out chemical signals (namely IL-12) that activate cytotoxic T cells and natural killer (NK) cells. Inhibition of dendritic cell signaling effectively disarms this entire branch of the immune system.

Chemotherapy can cause further damage because it can be very damaging to the stem cells in the bone marrow.

In a sense, the immune systems of people getting chemotherapy are slammed from both sides: the cancer itself blinds T cells and NK cells, and the drug-induced myelosuppression diminishes immune cell counts. Reversing and restoring suppressed immune function is an essential aspect of cancer care.

AHCC increases the number of dendritic cells and their ability to stimulate the rest of the immune system. It increases production of IL-12 and IFN-γ.

In addition, AHCC specifically increases the activity of NK cells in cancer patients. "The combined effect is to unchain the immune system and to allow it to respond to, and destroy, cancerous cells," Dr. Alschuler said. These immune-mediated anti-tumor effects have been demonstrated against melanoma and lymphoma cancer cells in tumor-bearing rodents.

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The immune enhancing effect of AHCC is reason enough to consider it for patients needing immunosuppressive chemotherapy. It is particularly helpful in conjunction with cisplatin, one of the most common drugs for solid tumors. Cisplatin causes nausea, kidney damage, nerve damage, hearing loss, and overall malaise, making treatment quite distressing for patients. The side-effect burden sometimes limits the dose and duration, thereby decreasing efficacy.

Researchers in Japan have reported some preliminary findings that further support the syngergistic role of AHCC and many other chemotherapy agents including 5-fluorouracil, paclitaxel (Taxol), cyclophosphamide (cytoxan), 6-mercaptopurine (Purinethol), methotrexate, and cytosine arabinoside (Ara-C).

Human studies are bearing out the expectations set by the animal trials. Dr. Reiki Ishizuka of the Tajima Clinic in Sapporo, has reported on increased survival and improved quality of life in patients with lung, breast and colon cancers who were taking AHCC along with their conventional chemotherapy treatments. Those taking AHCC had improved immune function. Although these findings are preliminary, there is a growing body of evidence to support the use of AHCC along with chemotherapy – to improve its benefits and to reduce its side effects.