Cartilage and Nutriceutical Update

Stephen Holt, M.D.

The health care profession and patients continue to await solid evidence about the effects of shark or bovine cartilage in the treatment of angiogenesis-dependent disease states,[1] Some evidence has accrued that shark cartilage *may* have efficacy in several common diseases, including but not limited to cancer. Zealots have made unsubstantiated claims about the benefits of therapy with shark and other types of cartilage, whereas skeptics have ridiculed apparent beneficial therapeutic observations with shark cartilage products. Although many observations of the beneficial effects of shark cartilage have been considered anecdotal, overall, I believe that a number of these observations are not explicable by chance alone. These prevailing contentions are the main reason an in-depth review of cartilage therapy should be commissioned. The manufacturers of shark cartilage who are selling cumulatively up to 50 million dollars of product worldwide should fund objective research.

In October 1995, a group of scientists and clinicians assembled in Elmsford, New York, to review the current evidence for the safety and efficacy of shark and bovine cartilage in disease management and to determine new directions for cartilage research. This scientific meeting was led by Abraham Mittelman, M.D., of New York Medical College, Valhalla. My un-published review of the world literature on shark cartilage provided a framework for discussion at the meeting. This meeting identified several issues, including the need for further controlled clinical trials of cartilage products in angiogenesis-dependent disease states and more basic science research to identify the active constituents of cartilage and their putative in vivo effects. The panel of scientists thought that early observations, in pilot trials, of shark cartilage for osteoarthritis were promising enough to justify larger-scale clinical trials to investigate potential efficacy. The notion that shark or bovine cartilage is effective in cancer treatment was regarded as still "unsubstantiated" by the group. I agree with this conclusion.

Ongoing Clinical Trials of Cartilage in Cancer

Several general issues require a discussion in relationship to current ongoing clinical trials of shark cartilage. A double standard may exist in clinical trials of unconventional or alternative therapies for disease states. Several repressive issues appear to have been identified by alternative health care physicians in relationship to the evolution of alternative cancer therapies. Foremost in this line of reasoning is the concern that orthodox medical institutions have an edge with the regulatory agencies, such as the Food and Drug Administration (FDA), that supervise medical research activity. There are unfortunate time displacement issues where alternative therapy is often attempted only after conventional medical therapy has failed. This situation creates a potential bias against the assessment of the efficacy of such alternative medical approaches. Like it or not, the conventional mode of therapy is considered the accepted option, and if one accepts this reasoning, alternative medical strategies (e.g., nutrients, botanicals, homeopathic remedies) are by their very nature at best alternative or secondary. Although the perceptions of the regulatory affairs establishments may have been too austere in the mid 1980s, these regulatory' bodies have commendably started to change their approach to alternative or contemporary therapy and the practice of alter-native medicine in general.

Recently, the FDA has not lived up to its repressive label. The agency must be appreciated for its approval of at least four phase 11 protocols that are under wav to assess the safety and efficacy of shark cartilage for the treatment of cancer. These protocols include: Cartilage Technologies, Inc., phase II assessment of shark cartilage brand Cartilade® in advanced cancer 1993, Simone phase II studies with shark cartilage brand Selachii 490 in advanced cancer 1994, Lane phase II studies with shark cartilage brand Benefin® in cancer and Kaposi's sarcoma 1995, and Cancer Treatment Centers of America's study with Cartilade® in various advanced cancers 1995. Information on these current FDA-approved studies are not in the public realm.

The protocol produced by Cartilage Technologies, Inc., is being undertaken by Michael Rothkopf. M.D., and an oncology group headed by Stewart Leitner, M.D., of St Barnabas Hospital in Livingston, New Jersey. This protocol involves the application of shark cartilage (Cartilade® to patients with advanced prostate or breast cancer who have failed traditional therapies, including radiation or chemotherapy, alone or in combination. The results of this trial are eagerly awaited, since this form of shark cartilage has been used in most published studies, and it was used in the widely reported Cuban clinical trials.[2]

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Charles Simone, M.D.'s (Simone Medical Center, Piscataway, New Jersey), protocol involves the administration of shark cartilage (Selachii brand), but it is combined with a ten-point lifestyle program that has been proposed by Dr. Simone to be intrinsically beneficial in itself. However. Dr. Simone's studies with shark cartilage may add further confusion in the assessment of the safety and efficacy of shark cartilage because the added lifestyle program could confound the results. One of the major alleged benefits of shark cartilage therapy is an enhancement in the quality of life of treated patients with advanced cancer. Therefore, the addition of a lifestyle program to a clinical trial protocol for shark cartilage may make an analysis of the data problematic.[2]

The recently filed investigational new drug (IND) application by I. William Lane, Ph.D., in 1995 for Benefin® is a protocol that is directed against advanced cancer and Kaposi's sarcoma. Kaposi's sarcoma is a tumor of vascular origin that is resistant to many forms of conventional medical therapy. This neoplasm is a good choice of a recalcitrant cancer that should respond, in theory, to antiangiogenic therapy because it is a primary tumor of blood vessels. Indeed, a recent report of a response of Kaposi's sarcoma to direct current electricity, which is believed to be antiangiogenic, adds further rationale to the application of antiangiogenic therapy for this disorder.[3] A subsidiary of the Cancer Treatment Centers of America, the Cancer Research Institute, is using Cartilade® in an independent assessment of cartilage in cancer therapy. Individual physicians are said to have filed an IND application to test Cartilade® as an anticancer compound for various tumors.

Some results have emerged on the safety and efficacy of bovine tracheal cartilage in patients with advanced renal cell cancer primary renal cell cancer exhibits a predilection for metastases by hematogenous spread This neoplasm often grows directly into renal veins. Renal cancer is highly vascular in its typical form and can produce characteristic "cannonball" metastases For these reasons, this neoplasm is presumed to be an ideal candidate disorder for therapy with antiangiogenic potential Puccio et al. reported partial responses in 3 of 22 patients with renal cancer treated with bovine cartilage. The therapy appeared to be well tolerated in this pilot study, and the results seemed to suggest that bovine tracheal cartilage (catrix) may be active, on occasion, in previously untreated patients with metastatic renal cell cancer.[4]

The concern exists that further confusion in the assessment of the benefit, or lack thereof, of shark cartilage in advanced cancer could occur if any early data in phase 11 trials are disclosed. Such disclosure is, of course, illegal. The filing of an IND with the FDA must be assumed to be an indication of an intent by the individuals concerned to seek the answer to an unresolved scientific issue in a legitimate manner. However, the process of filing alone should not be interpreted as any endorsement by the regulatory authorities of the safety or efficacy of the agent in question Therefore, the "jury remains out" as far as the benefit of shark cartilage is concerned for the treatment of cancer.

The Versatile Biopharmaceutical Effects of Genistein, A Soya Isoflavone, with Key Supporting References

Anticancer activity in vitro

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Anticancer activity in *vivo*

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Angiogenesis inhibition

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Antioxidant activity

Nalm, M., Gestetner. B., Bondi, A., Birk, V. *Antioxidative and antihemolytic activities of soybean isoflavones*.J. Agr Food Chem 24:1174- 1177, 1976.

Inhibition of topoisomerase

Okura, A., Arakawa, H., Oka, H., Yoshiman, T., Monden, Y. *Effect of genistein on topoisomerase activity and on the growth of [val 12] Ha-ras-transformed NIH 3T3 cells*. Biochem Biophys Res *Commun* I 57: 183-189, 1988.

Inhibition of protein tyrosine kinases

Akiyama, T., Ogawaia, H. *Use and specificity of genistein as inhibitor of protein tyrosine kinases*. Meth Enzymol 201:362-370, 1991.

Differential induction

Kiguchi, K., Conscantinov, A.I., Huberman, E. *Genistein induced cell differentiation and protein-linked DNA strand breakage in human melanoma cells.* Cancer Commun 2:271-277, 1990.

Estrogenic activity

Biggers, J.D. *Plant phenois possessing estrogenic activity*. In: Fairbairn, J.W. (ed.), *The Phamocology of Plant Phenolics*. New York; Academic Press, 1959, pp. 51-69.

Natural Modulators of Angiogenesis

Not enough attention has been focused on the characterization of modulators of antiangiogenic from natural sources. Several antiangiogenic compounds of natural origin have been discovered in addition to those found in cartilage. The

angiogenesis inhibitor that has been isolated from cartilage is collagenase inhibitor, which had been previously identified, sequenced, and cloned from other sources. It has been called a tissue inhibitor of metalloproteinases. It is notable that this tissue inhibitor of metalloproteinases is one of the most potent antiangiogenic compounds isolated to date. Other natural antiangiogenic compounds include vitamin D_3 analogs, fumigallin (angioinhibins), herbimycin A, and genistein, This list of antiangiogenic substances of natural origin is growing rapidly.

Genistein is a very exciting, naturally occurring antiangiogenic compound. It is the main isoflavone found in soya beans. Genistein has demonstrable direct tumoricidal properties against several tumor types by virtue of its potent inhibition of protein kinase and other key enzymes that are involved in tumor growth. In addition, genistein may play a potential role in favorable differentiation of anaplastic malignancy to a less malignant type. A further potential benefit of genistein in cancer, and perhaps aging, is its powerful antioxidant effect, a property that is shared by other sova isoflavones. The potential anticancer application and the versatility of genistein have led to the development of a nutrient product derived from soya beans to be used as a dietary supplement, Genista®, for which no treatment claims have been made.

Isoflavones of soya origin are among the most exciting nutrients with versatile health benefits. Genistein is being subjected to intense research. Charles Day, M.D., a researcher in Louisville, Kentucky, has been working on a process of purifying soya isoflavones. Dr. Day stated that "soybean isoflavones are currently receiving a great deal of attention in the world scientific literature. The isoflavones genistin and genistein are being investigated for their possible beneficial effects on a variety of cancers, such as breast and prostate cancer, and as a treatment for osteoporosis. With all this attention, it could be asked why such a beneficial food material has not been marketed as a nutritional supplement in a concentrated format. The answer is that, until now, the cost of pure genistein has been prohibitive." Stephen Barnes, M.D., a leading researcher at the University of Alabama, is concerned about the safety of pure genistein in a pill because of its powerful biological effects.

There is substantial interest in the use of soya protein products containing isoflavones as dietary supplements (Genista®: for information contact CartiLife, New York, NY, (800) 227-8454; Life Services Supplements Inc., Neptune, NJ, (800) 542-3230; Purity Life Health Products Ltd., Acton, Ontario, Canada, (800) 265-2615, (800) 665-8830; AER Health. UK.01424 883126; Health Innovations, UK, 01204 84O342).

The combined interest in the angiogenic properties of shark cartilage and the similar but apparently more powerful and versatile effects of soya isoflavones (genistein) has led to the development of a health drink containing both natural products. This product (Cartigen), which contains soya protein isolates (containing isoflavones) and shark cartilage, will be available in the new year from CartiLife. According to Michael Sullivan, the chief executive officer of CartiLife, pilot marketing and clinical tests of Cartigen are planned in several locations.

Ukrain

Ukrain is a semisynthetic derivative of alkaloids derived from the plant *Chelidonim majus* L.[5] This plant-derived alkaloid is conjugated with thiophosphoric acid to produce Ukrain. Ukrain has been shown to have immunomodulatory activity in cancer patients, and in vitro it has demonstrated toxic effects on malignant cells.[4] This compound is currently under research and development for cancer therapy. Early clinical observations of its use in cancer patients appear promising. Ukrain appears to increase oxygen consumption in normal and cancer cells. Oxygen consumption returns to normal in nonmalignant cells within 15 minutes, whereas it falls irreversibly to zero in cancer cells. In addition, Ukrain has been found to decrease DNA, RNA, and protein synthesis in malignant cells.

Ukrain has been tested in 60 human cancer cell lines representing nine major types of cancer by the National Cancer institute, Bethesda, Maryland. In all cell lines, a near 100 percent growth inhibition was found at specific concentrations of Ukrain. Further interesting features of Ukrain are its ability to selectively localize in malignant tissues and its ability to fluoresce when light of specific wavelength is applied to tissue containing Ukrain. Robert Atkins, M.D., of the Atkins Center, New York, described Ukrain as, "one of the most exciting and promising breakthroughs in cancer treatment that requires much further research."

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