



Best of Naturopathy

An In-Office Evaluation of Four Dietary Supplements on Natural Killer Cell Activity

by James Belanger, ND, MT

Abstract:

The natural killer (NK) cell activity blood test is useful in predicting the prognosis of a cancer patient. The purpose of this in-office, nonrandomized open-label trial was to determine whether four different dietary supplements commonly sold in health food stores and over the Internet, consistently and statistically affected NK cell activity in cancer patients. Thirty-four patients were assigned to one of four groups: Group A was given 1-3g/day of modified arabinoxylane with meals. Group B was given 6000mg/day of coriolus mushroom. Group C was given 4g/day of antigen-infused dialyzable bovine colostrum/whey extract and group D was given 3-6g/day of active hexose correlated compound (AHCC). NK cell activities were assessed before treatment and after an average of 16 weeks of therapy. AHCC was the only supplement that consistently and statistically increased NK cell activity. The average increase was 249%. Modified arabinoxylane statistically increased NK cell activity, but did not consistently help every patient. No side effects were encountered during the study period in any of the four groups.

Introduction

Despite recent advances in oncology, a substantial amount of people with cancer are dying in less than five years (See table 1).¹

To help improve these survival rates it may be important to identify and correct various adverse prognostic indicators. One negative prognostic indicator is low natural killer (NK) cell activity. Natural killer cells comprise between 5–20% of the peripheral blood lymphocytes and are capable of recognizing and killing tumor cells that completely lack expression of MHC Class I and II antigens.² The ability of a cancer patient's NK cells to lyse cancer cells can be determined by a 4-hr ⁵¹chromium-release assay. Studies have shown that cancer patients with a low activity of NK cells have shorter remissions, greater tumor burdens and an increased risk for nodal metastasis. Response rates to chemotherapy may be lower and recurrence rates after surgery may be higher in patients with low baseline NK cell activities. It is also not uncommon for the activity of NK cells to decrease just prior to a recurrence in a patient's cancer.³⁻²²

It may be possible to improve a cancer patient's prognosis by maintaining a high

NK cell activity level. Several studies have demonstrated improved survival rates after activated killer cells are transferred into cancer patients. Transplanting activated killer cells into people, however, may create unwanted side effects,^{23,24} therefore, activating the natural killer cells via an oral route may be a better choice. Various natural substances such as coriolus mushroom, active hexose correlated compound (AHCC), modified arabinoxylane and antigen-infused dialyzable bovine colostrum/whey extract have been described as oral NK cell activators in articles and advertisements. The purpose of this in-office study was to determine if these products consistently and significantly affected NK cell activity in cancer patients as advertised.

Material and Methods

Patients

This study was a nonrandomized, open-label trial in patients with a cancer diagnosis and was carried out in the author's office beginning in 2002. Thirty-six patients completed the study, but two were dropped from the statistical analysis because they were both taking high doses of fish oil and borage oil. Studies have shown that high doses of these oils severely decrease NK cell activity by decreasing levels of leukotriene-B₄, a strong NK cell activator.^{25,26} The 34 patients analyzed had various types of cancer in different stages. They consisted of 26 females and 8 males ranging from two to 72 years of age. None of the patients were taking a NK cell activator prior to the commencement of the study. The patients were divided into 4 groups. Group A, consisting of 15 patients, was treated with modified arabinoxylane. Group B, consisting of 8 patients, was treated with coriolus mushroom. Group C, consisting of 3 patients, was treated with antigen-infused dialyzable bovine colostrum/

Table 1: 1995-2000 5-Year Survival Rates (%) of Conventionally-Treated Cancer Patients

| Type of Cancer | Localized | Regional | Distant |
|----------------------------|-----------|----------|---------|
| Melanoma | 97.6 | 60.3 | 16.2 |
| Breast | 97.5 | 80.4 | 25.5 |
| Bladder | 94.1 | 48.8 | 5.5 |
| Ovarian | 93.5 | 68.8 | 28.5 |
| Kidney | 91.1 | 59.1 | 9.3 |
| Colorectal | 89.9 | 67.3 | 9.6 |
| Oral Cavity & Pharynx | 81.0 | 50.7 | 29.5 |
| Non Small Cell Lung Cancer | 51.3 | 17.0 | 2.2 |
| Small Cell Lung Cancer | 21.4 | 10.8 | 2.1 |
| Pancreas | 15.2 | 6.8 | 1.8 |

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whey extract and group D, consisting of 8 patients, was treated with AHCC. Each group was allowed to take other nutritional supplements during the test period. Many of the same supplements were taken amongst the four groups. None of the allowed nutritional supplements, however, have been demonstrated to increase NK cell activity.

Modified arabinoxylane Group (Group A: n=15)

Modified arabinoxylane is a polysaccharide from rice bran that contains beta 1,4-xylopyranose hemicellulose that has been enzymatically treated with an extract from hyphomycetes mycelia (shiitake mushroom). Modified arabinoxylane was given in either a caplet or capsule form in a dose of 1000mg three times daily with meals and two hours away from other supplements. If the patient was taking the product longer than two months, the dose was reduced to 1000mg once daily with food. Modified arabinoxylane was chosen for this study because one human trial showed this substance increased NK cell activity by five-fold in 24 healthy individuals after eight weeks of treatment.²⁷

Coriolus Group (Group B: n=8)

Coriolus versicolor is a mushroom commonly used in traditional Chinese and Japanese medicine. Hot water extracts of this mushroom contain 1-4, 1-3 polysaccharides (beta glucans) which are described to have immunomodulating properties.²⁸⁻³⁰

The coriolus product used in this study contained both the mycelium and young fruit body of the coriolus versicolor mushroom. Each 500mg tablet of Coriolus was standardized for about 63mg of protein-bound polysaccharides. Each patient in this group was given a dose of 2000mg three times a day with meals to provide a total of 756mg/day of protein-bound polysaccharides.

Antigen-Infused Dialyzable Bovine Colostrum/Whey Extract Group (Group C: n=3)

Antigen-Infused Dialyzable Bovine Colostrum/Whey Extract is an extract of the low molecular weight molecules naturally found in bovine whey. Cows are infused with antigens shortly before parturition. After delivery, the colostrum is collected and filtered to completely remove

the whey proteins, antibodies and other higher-molecular weight molecules.^{31,32} The author chose this product after reading material describing this substance as a powerful NK cell activator. Each capsule used in this study contained 50mg of Antigen-Infused Dialyzable Bovine Colostrum/Whey Extract, 150mg of arabinogalactan, 25mg of astragalus root and 25mg of maitake mushroom 4:1. Patients were instructed to take four capsules twice a day with food for a total of 400mg/day of Antigen-Infused Dialyzable Bovine Colostrum/Whey Extract.

AHCC Group (Group D: n=8)

Active hexose correlated compound or AHCC contains a mixture of low molecular weight oligosaccharides enzymatically extracted from a myceloid of several species of Basidiomycete mushrooms including shiitake, which are cultured in a liquid medium with rice bran. Three grams per day of AHCC was demonstrated in one human trial to increase NK cell activity an average of 2.5-fold in nine out of eleven cancer patients after two weeks of therapy.³³ Each patient in this group took 2000mg of AHCC three times

Table 2: Effects of Modified Arabinoxylane on NK Cell Activity in Cancer Patients (Group A)

| Age | Sex | Cancer Type & Stage | Concurrent Chemotherapy | Before | After | Difference | # of Weeks |
|------|-----|-----------------------------|-------------------------|--------|-------|------------|------------|
| 48 | ♀ | Breast Cancer, Stage IV | Yes | 8.0 | 5.6 | -2.4 | 28 |
| 58 | ♀ | Hodgkins Disease, Stage IIA | Yes | 26.9 | 11 | -15.9 | 5 |
| 49 | ♀ | Breast Cancer, Stage I | No | 8.2 | 4 | -4.2 | 50 |
| 41 | ♀ | Breast Cancer, Stage 0 | No | 14.6 | 13.4 | -1.2 | 4 |
| 47 | ♀ | Breast Cancer, Stage I | No | 24.2 | 27.9 | 3.7 | 8 |
| 48 | ♂ | CLL, Stage I | No | 7.3 | 9.5 | 2.2 | 25 |
| 37 | ♂ | NSCLC, Stage IIIA | Yes | 5.5 | 15.1 | 9.6 | 14 |
| 71 | ♂ | Prostate Cancer, Stage IV | No | 21.2 | 24 | 2.8 | 35 |
| 75 | ♀ | ALL w/ Brain Metastases | Yes | 9.2 | 20 | 10.8 | 5.5 |
| 64 | ♀ | Breast Cancer, Stage I | No | 10.6 | 11 | 0.4 | 8 |
| 39 | ♂ | Liposarcoma, Stage IV | Yes | 5.0 | 5.7 | 0.7 | 8 |
| 75 | ♂ | Glioblastoma multiforme | Yes | 2.6 | 13.2 | 10.6 | 6 |
| 49 | ♀ | Breast Cancer, Stage IIB | Yes | 8.0 | 29.6 | 21.6 | 14 |
| 50 | ♀ | Ovarian Cancer, Stage IV | Yes | 4.2 | 22.2 | 18 | 8 |
| 47 | ♀ | Breast Cancer, Stage IIB | Yes | 5.0 | 20.1 | 15.1 | 6 |
| Mean | | | | 10.70 | 15.49 | 4.79* | 15 |
| SD | | | | 7.58 | 8.12 | 9.64 | |

*P<0.10

Table 3: Effects of Coriolus Mushroom on NK Cell Activity in Cancer Patients (Group B)

| Age | Sex | Cancer Type & Stage | Concurrent Chemotherapy | Before | After | Difference | # of Weeks |
|------|-----|--------------------------|-------------------------|--------|-------|------------|------------|
| 52 | ♀ | Breast Cancer, Stage IIB | No | 11.8 | 8.8 | -3.0 | 4 |
| 72 | ♀ | Breast Cancer, Stage I | No | 22.6 | 18.4 | -4.2 | 12 |
| 47 | ♀ | Breast Cancer, Stage IIB | No | 6.5 | 5.0 | -1.5 | 4 |
| 55 | ♂ | Bladder Cancer, Stage II | No | 17.7 | 12.1 | -5.6 | 9 |
| 49 | ♀ | Breast Cancer, Stage I | No | 9.2 | 12.7 | 3.5 | 9 |
| 41 | ♀ | Breast Cancer, Stage 0 | No | 13.8 | 14.6 | 0.8 | 8 |
| 72 | ♀ | Non-Hodgkins, Stage I | No | 14.2 | 17.1 | 2.9 | 19 |
| 47 | ♀ | Breast Cancer, Stage I | No | 8.2 | 9.7 | 1.5 | 5 |
| Mean | | | | 13.00 | 12.30 | -0.70* | 9 |
| SD | | | | 5.31 | 4.44 | 3.38 | |

*Not significant

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a day with meals. If they were taking the product longer than two months, the dose was reduced to 1000mg three times a day with food.

NK cell cytotoxicity assay

All patients had blood drawn before they began taking their assigned product to determine their baseline NK cell activity. All NK cell cytotoxicity assays were performed by Immunosciences Lab, Inc (Beverly Hills, California) using a standard 4-hr ⁵¹Cr-release assay as described by

Vojdani et al. 2004.³⁴ The results of NK cell assays were expressed in terms of lytic units (LU) calculated as described by Whiteside et al (1990).³⁵ Normal ranges for this test are between 20-50 lytic units.

Compliance

Compliance was determined by how often patients purchased their supplements from the author's office using Quickbooks software and through patients' verbal confirmation. Every patient chosen for this study was fully compliant.

Statistics

The data was analyzed statistically by the paired-t test.

Results

As shown in Table 2, the average increase in NK cell activity in the modified arabinoxylane group as a whole was significant, but the results varied considerably between patients. Modified arabinoxylane tripled NK cell activity in only four out of the fifteen patients in this group. The NK cell activity in 27% of patients actually decreased despite taking the recommended dose for an average of 15 weeks (4-50 weeks). Many of these patients were not on chemotherapy.

As shown in Tables 3&4, no significant changes were observed in NK cell activity in the patients given coriolus mushroom or antigen-infused dialyzable bovine colostrum/whey extract. Fifty percent of patients in fact, had a decrease in NK cell activity after an average of nine weeks on coriolus. Two out of the three patients given antigen-infused dialyzable bovine colostrum/whey extract had a decrease in NK cell activity after taking 400mg/day for an average of 7.5 weeks (4-7 weeks).

AHCC was the only product that consistently and significantly increased NK cell activity in all patients including those on chemotherapy. (See Table 5.) The average increase was 249% (166-469%) after a mean of 8 weeks (3-14 weeks).

No side effects were reported in any patient on any of the four treatments during the experimental period.

Discussion

Monitoring NK cell activity during follow-up office visits and correcting abnormalities with an oral NK cell activator may increase survival rates in cancer patients in remission and may prevent cancer occurrences in high risk groups.^{3-22, 28-30} Strayer et al. reported that NK cell activities are consistently lower in people with a family history of cancer compared to individuals with a low familial incidence of cancer. Strayer et al. also reported that NK activity is inversely related to the number of family members with cancer.³⁶ Nakajima et al. reported that patients with cirrhosis of the liver have a higher risk of hepatocellular carcinoma if their NK cell activities are low.³⁷ In an eleven year study of 2196 women, Imai et al. found that

Table 4: Effects of Antigen-Infused Dialyzable Bovine Colostrum/Whey Extract on NK Cell Activity in Cancer Patients (Group C)

| Age | Sex | Cancer Type & Stage | Concurrent Chemotherapy | Before | After | Difference | # of Weeks |
|------|-----|-----------------------------|-------------------------|--------|-------|------------|------------|
| 58 | ♀ | Hodgkins Disease, Stage IIA | Yes | 11.0 | 7.0 | -4.0 | 4 |
| 52 | ♀ | Breast Cancer, Stage IIB | Yes | 8.8 | 10.2 | 1.4 | 20 |
| 47 | ♀ | Breast Cancer, Stage IIB | No | 13.1 | 6.5 | -6.6 | 7 |
| Mean | | | | 10.97 | 7.90 | -3.07* | 10 |
| SD | | | | 2.15 | 2.01 | 4.08 | |

*Not significant

Table 5: Effects of AHCC on NK Cell Activity in Cancer Patients (Group D)

| Age | Sex | Cancer Type & Stage | Concurrent Chemotherapy | Before | After | Difference | # of Weeks |
|------|-----|-----------------------------|-------------------------|--------|-------|------------|------------|
| 41 | ♂ | NSCLC, Stage IV | Yes | 2.9 | 13.6 | 10.7 | 7 |
| 2 | ♀ | Rhabdomyosarcoma, Stage IV | Yes | 8.4 | 25.4 | 17 | 14 |
| 70 | ♀ | Breast Cancer, Stage I | No | 14.7 | 57.6 | 42.9 | 3 |
| 47 | ♀ | Breast Cancer, Stage I | No | 9.7 | 16.8 | 7.1 | 4 |
| 58 | ♀ | Hodgkins Disease, Stage IIA | Yes | 7 | 14.4 | 7.4 | 6 |
| 53 | ♀ | Desmoid Tumor, Stage I | Yes | 22.3 | 41.8 | 19.5 | 8 |
| 61 | ♂ | Leiomyosarcoma, Stage IV | Yes | 11.4 | 18.9 | 7.5 | 11 |
| 47 | ♀ | Breast Cancer, Stage IV | Yes | 16.2 | 42.4 | 26.2 | 11 |
| Mean | | | | 11.58 | 28.86 | 17.29* | 8 |
| SD | | | | 6.05 | 16.37 | 12.43 | |

*P<0.01

Table 6: Average Monthly Retail Cost of Four Dietary Supplements for the Immune System

| | Modified Arabinogalactan | Coriolus | Antigen-Infused Dialyzable Bovine Colostrum/Whey Extract | AHCC |
|----------------|----------------------------------|---------------|--|----------------------------|
| Dose:Cost (\$) | 1g/day: 208.50 3g/day: 625.50 | 6g/day: 99.80 | 400mg/day: 264 | 3g/day: 300 6g/day: 600 |

women with a high NK cytotoxic activity (>51%) had approximately half the risk of cancer compared with those with a low NK cytotoxic activity ($\leq 34\%$).³⁸

In this study, only AHCC significantly and consistently increased NK cell activity levels in cancer patients. Modified arabinogalactan statistically increased NK cell activity, but results were not consistent in every patient. Coriolus mushroom and antigen-infused dialyzable bovine colostrum/whey extract did not consistently or significantly increase NK cell activity. These findings are a concern for a number of reasons. Table 6 shows the average retail price of these supplements per month.

These are expensive prices for patients to pay for products that may not be as beneficial as claimed in advertisements. Advertisements from companies over the internet, in health food stores and in magazines may mislead patients into thinking the product will help their natural killer cells. Doctors may also prescribe these supplements without verifying the product's efficacy.

There is no doubt that coriolus mushroom extracts have a place in the treatment of cancer patients. Numerous human trials have been done and results have shown that coriolus may increase survival rates in cancer patients.^{28-30,39} Most studies published in peer-reviewed journals, however, have been done on Krestin, protein-bound polysaccharide K, extracted from the mycelia of coriolus versicolor, not on other brands. Krestin is also the only extract of coriolus listed on medline which has been shown to increase NK cell activity in cancer patients.⁴⁰ Other manufacturers of coriolus often transfer the results found in Krestin research onto their product even though the two forms of coriolus are not identical. A coriolus extract other than Krestin was used in this study to confirm product efficacy and to verify claims made by the manufacturer.

Shortcomings of this study were as follows: Sample size was small in each group, but represented 29 cancer patients with abnormally low NK cell activities (<20 lytic units) who needed a reliable product to help them. Many patients were taking other nutritional supplements and/or chemotherapy on the same days as the test products. It is possible that these other substances could have interfered with the results. In the clinical world, however, cancer patients are rarely on

one medication or nutritional supplement. Because of the complexities of cancer, it is most effectively treated with combination therapy that addresses growth factors, angiogenesis and cellular replication as well as the immune system. A good NK cell activator needs to be able to work even in the midst of other therapies. The only product that consistently increased NK cell activity despite the use of multiple nutritional supplements and concurrent chemotherapy was AHCC.

The dose of antigen-infused dialyzable bovine colostrum/whey extract used in this study was lower than the 600-800mg/day recommended by Stoff.³² Some manufacturers of this product, however, recommend 100mg/day of antigen-infused dialyzable bovine colostrum/whey extract in conjunction with astragalus, maitake and arabinogalactan, which will support healthy natural killer cell levels. The dose used in this study, therefore, was chosen to lie in between these two recommendations.

NK cell activity can be affected by a variety of factors including depression, lack of social support,⁴¹ high fat diets (>20% of total calories, including unsaturated fats),⁴² age and exercise levels.⁴³ Patients in this study, however, kept their diet and exercise routines consistent. Everyone also had a good support system and did not suffer from major depression.

Critics may say that the NK cell activity is not reliable because it frequently fluctuates. This statement, to the author's knowledge, has not been verified by any published clinical studies. In fact, many studies show that the standard 4-hr ⁵¹Cr-release assay is very accurate as long it is done properly and the data is expressed appropriately.⁴⁴ Critics may also say that the activities of NK cells in an assay are different from their activities in the human body. Numerous clinical studies, however, show there is a relationship between the 4-hr ⁵¹Cr-release NK cell assay and prognosis, tumor burden and risk of metastasis in cancer patients.³⁻²²

Three other products touted as NK cell activators, inositol hexaphosphate with inositol, maitake extract and larch arabinogalactan, were not used in this study for the following reason. Other patients not included in this study were taking these products consistently for several months before baseline NK cell activities were done. These patients happened to have extremely low NK cell activities at baseline

despite taking the suggested doses of inositol hexaphosphate with inositol, maitake extract or larch arabinogalactan for several months.

Conclusion

Despite today's advances in oncology, many people with early stage cancers are dying in less than five years. Clearly, advances need to be made in cancer therapeutics. Activating natural killer cells with an oral agent may be one therapy that can improve these survival rates.^{28-30,40,45} This study found only AHCC to be a consistent natural killer cell activator even when combined with chemotherapy and other nutritional supplements. More studies, however, need to be done to see if AHCC is effective at decreasing recurrence rates and increasing survival rates in early stage cancer patients in remission. The author knows of only one study so far looking at AHCC and prognosis that has been published. This study found that AHCC improved survival rates in postoperative hepatocellular carcinoma patients. This study, however, was not randomized and therefore, results may have been influenced by self-selection bias.⁴⁵ Krestin is also another product that shows a lot of promise. Follow-up immune system testing, however, should be done if one is using Krestin or another coriolus product.

In conclusion, all doctors should monitor NK cell activity whenever prescribing a product claiming to be a natural killer cell stimulant even if it is AHCC. Increasing NK cell activity may improve a cancer patient's prognosis. The study author has used this test over and over and has to date, never seen an early stage cancer patient in remission have a recurrence if their NK cell activity was normalized.

About the author: James T. Belanger, ND received his BS from the University of Massachusetts and his ND from Bastyr University. He is the secretary of the Massachusetts Society of Naturopathic Doctors and the treasurer of the Oncology Association of Naturopathic Physicians. In addition to his private practice in Lexington, Massachusetts, he currently teaches nutrition at the New England School of Acupuncture. After surviving cancer himself, Dr. Belanger has studied oncology research in depth and has created a center in Lexington, Massachusetts, along with his wife Dr. Karen Braga, which focuses on the holistic care of people with cancer.

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