Evaluation of Shark Cartilage in Patients with Advanced Cancer

A North Central Cancer Treatment Group Trial

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BACKGROUND. Shark cartilage has been a popular complementary or alternative medicine intervention. The basis for this popularity is the claim that sharks rarely get cancer because of the high proportion of cartilage in the shark's body. However, early studies were equivocal. Therefore, a clinical trial was conducted to look at the impact of shark cartilage in patients with advanced cancer. The primary goal of this trial was to determine whether a shark cartilage product improved overall survival for patients with advanced cancer who were getting standard care. Secondary research goals were to evaluate toxicities, tolerability, and quality of life associated with this shark cartilage product.

METHODS. The study was a two-arm, randomized, placebo-controlled, double-blind, clinical trial. Patients with incurable breast or colorectal carcinoma had to have good performance status and organ function. Patients could be receiving chemotherapy. Patients were all to receive standard care and then to be randomly selected to receive either a shark cartilage product or an identical-appearing and smelling placebo 3 to 4 times each day.

RESULTS. Data on a total of 83 evaluable patients were analyzed. There was no difference in overall survival between patients receiving standard care plus a shark cartilage product versus standard care plus placebo. Likewise, there was no suggestion of improvement in quality of life for patients receiving the shark cartilage, compared with those receiving placebo.

CONCLUSION. This trial was unable to demonstrate any suggestion of efficacy for this shark cartilage product in patients with advanced cancer. ***Cancer* 2005;104: 176–82.** © *2005 American Cancer Society.*

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Much has been made in recent years of the mystical aura afforded the potential therapeutic effects of shark cartilage. Clearly, part of the impact can be attributed to a visceral fear of cancer combined with a healthy respect for a creature that has survived almost without

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evolutionary changes from prehistoric times. It has been reported that sharks rarely get cancer because one of their defining features is a body with a high proportion of cartilage. Logic has led some to believe that this must be the reason for sharks' relative health.[1] In 1991, clinicians reported that as many as 80% of their cancer patients had asked them about the efficacy of shark cartilage therapy.[2] The use of alternative therapies, such as shark cartilage, by cancer patients is widespread despite variable scientific evidence documenting their effectiveness. The responsibility of scientific endeavor, however, is to remove the mysticism and investigate the phenomenon in an objective and controlled environment.

Interest in shark cartilage stems from early research reported in two compelling studies. The first study involved glycoproteins isolated from hammerhead sharks. These glycoproteins extended life in leukemic mice.[3] The second study implanted shark cartilage pellets intraocularly in three rabbits, which resulted in inhibited tumor angiogenesis.[4] In vitro and pharmacokinetic studies have indicated that the mechanism of action for shark cartilage is through the prevention of neovascularization and subsequent inhibition of cell proliferation.[5–8] Evidence has also suggested that shark cartilage may protect against mutagenesis and DNA lesions.[9,10] Cytotoxic activity of shark peripheral blood leukocytes has also been reported.[11]

At the time of our initial study development, clinical evidence for shark cartilage benefit was sparse. One report came from a Cuban trial of 29 patients that reportedly produced a positive response rate of 20% (3 of 15 evaluable patients) to shark cartilage treatment, although some researchers have suggested that there were serious methodologic flaws in this trial.[12] An American study by Charles Simone of the Simone Protective Cancer Center also reported a positive response rate of 20% (4 of 20 patients) and further claimed that as many as 50% of treated patients experienced improved quality of life (QOL) and other ancillary benefits.[12] Finally, a Phase I/II study of 60 patients with various cancers showed no tumor response and considerable gastrointestinal toxicity.[13]

There have been several cautionary articles regarding naive and indiscriminate use of shark cartilage for treating cancer.[2,12,14,15] Most of these articles are brief editorials summarizing the appropriate argument that new cancer therapies need strict objective testing before they are accepted for widespread use. It was argued that there was no contradictory evidence regarding the potential efficacy of shark cartilage.[16]

In addition to the issue of efficacy, past studies raised questions concerning oral tolerability and toxicity that may be attributed to shark cartilage. Therefore, at the behest of the National Cancer Institute, the North Central Cancer Treatment Group (NCCTG) developed the current Phase III study to look at the impact of shark cartilage on survival, toxicity, and QOL in patients with advanced cancer.

MATERIALS AND METHODS

The current study was a two-armed, randomized, placebo-controlled, double-blinded, clinical trial. The primary goal of the study was to determine whether the addition of Benefin® Shark Cartilage (LaneLabs, Allendale, NJ) to standard therapy improved overall survival for patients with advanced cancer, compared with standard treatment plus placebo. The design involved a target total accrual of 660 patients to produce 600 evaluable observations (300 per treatment arm). A sample of 600 patients would provide 90% power to detect a 33% improvement in the primary outcome of median survival, assuming the placebo group had a median survival of 6 months.

Patients eligible for this clinical trial were men and women $>$ 18 years of age who had incurable breast or colorectal carcinoma. Study participants had to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2, a physician-judged life expectancy $>$ 3 months, and sufficient liver function. Further, patients could not have used shark cartilage within the previous 60 days and could not be on a concomitant clinical trial of cytotoxic chemotherapy. However, patients could have been receiving chemotherapy outside of a clinical trial. Patients with breast carcinoma must have had disease progression regardless of receiving two prior and distinct chemotherapy regimens. Potentially eligible patients underwent a history and physical examination and had to have had recent hematology and chemistry blood tests completed. All patients provided written informed consent according to federal guidelines.

Stratification included disease type (breast, colorectal female, colorectal male), age ($\leq$ 49 yrs, 50–69 yrs, $\geq$ 70 yrs), performance status (ECOG 0–1 vs. 2), current chemotherapy use (yes or no), and baseline QOL (Uniscale rating of $<$ 50%, 50–75%, $>$ 75%).

Patients were randomly selected to receive either active Benefin® Shark Cartilage versus an identical-appearing placebo. Treatment assignment was calculated by a dynamic allocation procedure[17] that balances the marginal distributions of the stratification factors between the treatment sequences. This method of randomization is standard for North Central Cancer Treatment Group (NCCTG) clinical trials and ensures the allocation is concealed before a patient is registered to the study. One of the defining

characteristics of the shark cartilage treatment was its strong fishy odor and taste. The odor was sufficiently strong to be observed by clinical staff passing by the storage area of the agents. Much discussion occurred during the development of the trial concerning methods to mask and deal with this issue. The placebo was purposely made to have a similar strong aroma and flavor to maintain blinding. The shark cartilage and matching placebo were supplied as a powder. The shark cartilage placebo was titrated upward, as tolerated, every 3 days beginning with 24 g (4 scoops per day), toward a goal of 96 g (16 scoops per day). The daily dose was divided into 3 or 4 servings per day to be taken 30 minutes before meals and was mixed with chilled beverages, either water or juice. This dose was decided upon in concert with the supplier of the product, LaneLabs, and National Cancer Institute colleagues. The study design allowed patients with any Grade 2 or higher toxicity associated with study treatment to reduce their dose by one level (three scoops per day). Patients were to stay on the study substance for as long as they could tolerate the treatment.

While on the study, participants were assessed in person or by telephone once a month by a clinician. This assessment included the evaluation of toxicity that was graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) to rate nausea, vomiting, diarrhea, constipation, mucositis, neutropenia, thrombocytopenia, and any renal, genitourinary, cardiovascular, pulmonary, or neurologic events. Patients also received chemistry and hematology blood tests at 1 month, and then afterwards at physician discretion, throughout the remainder of the study. Several self-reported questionnaires were completed weekly for the first month by participants and at 1-month intervals for the remainder of the study. These questionnaires included the Spitzer Uniscale,[18,19] the Symptom Distress Scale (SDS),[20] and the Linear Analogue Self Assessment (LASA)[21] items relating to patient QOL.

The Uniscale is a one-question measure that asks the patient to rate overall QOL by indicating in a rectangle whether their QOL is of lowest quality, highest quality, or somewhere in between.[19] The SDS is a scale that has been used extensively to assess persons who have cancer.[20] It employs a 5-point scale to assess 10 symptoms: nausea, mood, appetite, insomnia, pain, mobility, fatigue, bowel pattern, concentration, and appearance. LASA items have been validated as general measures of global QOL dimensional constructs in numerous settings.[22–26] A series of five LASA items have been constructed to evaluate five general areas of well being: physical, emotional, spiritual, intellectual, and overall well being. These questions have been validated at the Mayo Clinic for use in cancer patients.

The primary endpoint of median survival time from random selection to the study was compared across the two treatment groups using Kaplan–Meier survival curves and associated two-sided log rank testing.[27] Potentially confounding variables were incorporated into the analysis through Cox regression modeling. Secondary endpoints included toxicity and QOL (as measured by the self-report questionnaires and National Cancer Institute Common Toxicity Criteria (NCI CTC) toxicity ratings. Toxicity rates were compared across Benefin® Shark Cartilage and placebo groups through equality of binomial proportions testing. QOL parameters were plotted over time and the area under the curve (AUC) was calculated.[28,29] Missing data were treated in two ways throughout these analyses: average value carried forward and last value carried forward. Neither method proved superior, nor did using these methods effect the outcome that the AUC was not statistically different between arms. Linear models involving generalized estimating equations (GEE)[30,31] were used to investigate the impact of potential confounding covariates on the primary results. A subset analysis of patients who managed to complete 3 months of protocol treatment was also undertaken.

RESULTS

There were a total of 88 eligible patients, 43 receiving shark cartilage and 45 receiving placebo, randomly selected for this clinical trial from August 13, 2001 to June 13, 2003. Of these, 4 patients cancelled before receiving shark cartilage or placebo, and 1 patient did not complete any of the self-report questionnaires correctly. As a result, evaluable data are available on 42 patients taking shark cartilage and on 41 patients taking placebo. Because of a slower than predicted accrual, the NCCTG Data Monitoring Committee, having access to an interim statistical report and acting independently from the study investigators, decided that the study should be closed to further patient accrual in June 2003.

Baseline characteristics for the study participants were well balanced across arms (Table 1). There were no significant differences between groups in baseline demographics such as gender, race, age, or QOL scores.

After 1 week of treatment, 73% of patients remained on the Benefin® Shark Cartilage arm and 61% remained on the placebo arm. By 1 month, approximately 50% of patients remained on either arm. Only 10% of patients completed more than 6 months of

TABLE 1
Baseline Demographics

Patient characteristics	Percentage on shark cartilage (n = 42)	Percentage on placebo (n = 41)	P value
Age group			0.68
≤ 49	7	12	
50–59	52	54	
≥ 70	41	34	
Gender			0.75
Female	57	54	
Male	43	46	
Race			0.99
Black	2	2	
White	98	98	
Disease type			0.82
Breast	19	20	
Colorectal female	41	34	
Colorectal male	41	46	
Previous RT			0.63
Yes	35	30	
No	65	70	
Prior therapy			0.72
Yes	90	88	
No	10	13	
First ER status (breast only)			0.80
Positive	50	63	
Negative	25	25	
Unknown	25	13	
First PR status (breast only)			0.49
Positive	63	50	
Negative	13	38	
Unknown	25	13	
Baseline Uniscale			0.61
< 50	10	13	
50–75	27	35	
> 75	63	53	
GBU Index			0.72
Good	31	37	
Bad	12	7	
Unsure	57	56	

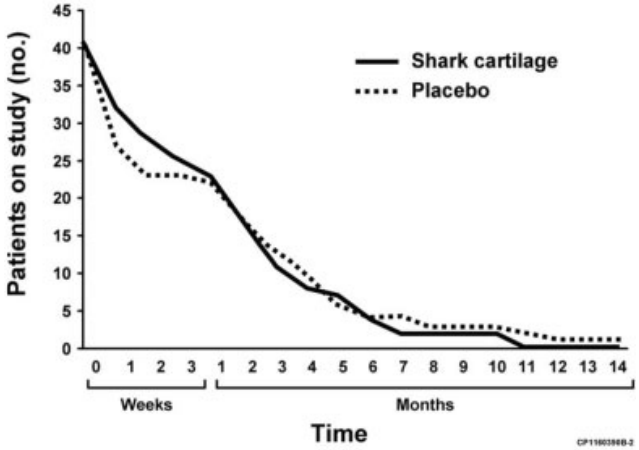

FIGURE 1. Time on study for the two protocol arms.

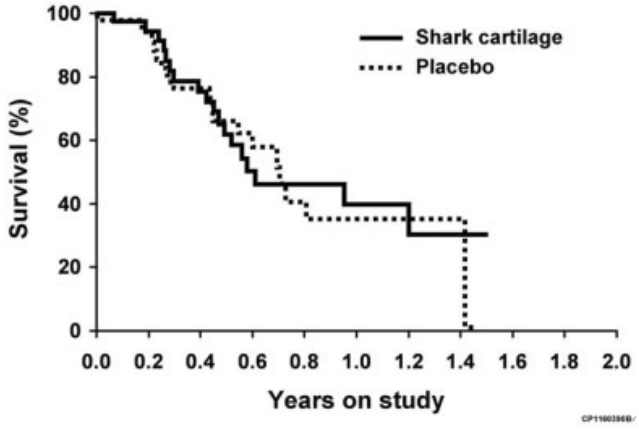

FIGURE 2. Survival curves for the two treatment arms.

treatment. One patient on the placebo arm completed 14 months (Fig. 1).

The primary endpoint of overall survival time from random selection was not statistically significantly different between treatment groups as assessed using Kaplan–Meier survival statistics (Fig. 2). Additionally, survival benefit was not detected between groups when split by concurrent medication and arm, nor by age group and arm. The GEE modeling confirmed results of univariate test procedures. The generalizability of the models was limited because of the resulting small sample size, so any conclusions on the impact of potentially confounding influences need to be considered with care.

The secondary endpoint of improved QOL was evaluated by comparing normalized AUC values of the Uniscale, SDS, and LASA questions. There were no statistically significant differences between arms for any of the assessments, although the AUC mean values in the placebo arm were higher on all 5 LASA questions and the overall SDS score. At 1 month from treatment initiation, QOL, as measured by the Uniscale, showed mean overall well being was 8 points worse in the patients receiving shark cartilage (P = 0.09)(Table 2). QOL as measured by the LASA at 1 month reflected a decreased mean overall well being score for patients receiving shark cartilage of 16 points on the 100-point scale (Table 3). This was statistically significant (P = 0.02) as well as clinically significant, as the score showed > 10 points difference on a scale from 0 to 100.[26] In the shark cartilage arm, for each time point up to and including 1 month, patients reported a decrease in QOL from their baseline scores for the 5 LASA questions and the total SDS score. Significant mean changes from baseline occurred between arms at Weeks 2, 3, and 4 for physical well being

TABLE 2
Uniscale Data (Month 1)

	Shark cartilage (n = 20)	Placebo (n = 19)	Total (n = 39)	P value
Uniscale				0.09
No.	20	19	39	
Mean (SD)	70 (16)	78 (17)	74 (17)	
Median	71	84	79	
Range	(38–95)	(41–95)	(38–95)	

SD: standard deviation.

TABLE 3
LASA Overall Well Being Item (Month 1)

	Shark cartilage (n = 23)	Placebo (n = 22)	Total (n = 45)	P value
Overall well being				0.02
No.	20	19	39	
Mean (SD)	70 (21)	86 (17)	78 (21)	
Median	75	100	75	
Range	(25–100)	(50–100)	(25–100)	

SD: standard deviation.

TABLE 4
LASA Physical Well Being—Mean Differences in Scores from Baseline

Difference	Shark cartilage mean (n = 42)	Placebo mean (n = 41)	P value
Baseline to Week 1	−10	2	0.06
Baseline to Week 2	−12	8	0.006
Baseline to Week 3	−13	8	0.006
Baseline to Month 1	−13	3	0.04

(Table 4). Patients on the shark cartilage arm had lower scores than baseline for the LASA physical well being scale, whereas the placebo arm had higher scores than baseline.

At Week 2, the shark cartilage arm decreased an average of 8 points, and the placebo arm increased an average of 6 points for emotional well being. This difference was statistically significant ($P = 0.02$) (Table 5). Many of the other changes were borderline significant with P values less than 0.1, indicating a cumulative tendency toward reduction of QOL among patients receiving shark cartilage. An O'Brien global test[32] including all of the QOL variables confirmed that the shark cartilage arm showed reduced QOL at Weeks 2 and 3 ($P = 0.005$ and $P = 0.05$ respectively).

Eleven patients remained on study after 3 months on the treatment arm, whereas 13 patients remained on the placebo arm. There is no statistically significant difference in Uniscale scores between arms for those

TABLE 5
LASA Emotional Well Being—Mean Differences in Scores from Baseline

Difference	Shark cartilage mean (n = 42)	Placebo mean (n = 41)	P value
Baseline to Week 1	−9	2	0.08
Baseline to Week 2	−8	6	0.02
Baseline to Week 3	−11	4	0.07
Baseline to Month 1	−7	2	0.24

patients who completed protocol therapy through Month 3. Patients on the shark cartilage arm reported a better outlook at Month 3 compared with those on the placebo arm ($P = 0.04$), as measured by the SDS instrument. Those patients also reported higher emotional and spiritual well being ($P = 0.05$ and 0.01 respectively) as captured by individual questions on the LASA. These results are reported with caution, given the very low number of patients in each arm at Month 3.

Toxicity experience was determined by clinician evaluation, and events were also reported through the SDS assessment. The majority of toxicities experienced were of Grade 1 or 2 in either arm. The most frequent Grade 3 toxicities on the shark cartilage arm were diarrhea ($n = 2$), dyspnea ($n = 3$), leukopenia ($n = 2$), neutropenia ($n = 5$), and bone pain ($n = 2$). None of these severe toxicities were experienced on the placebo arm. The most frequent Grade 3 toxicities on the placebo arm included fatigue ($n = 2$), neurosensory ($n = 2$), and rectal bleeding ($n = 2$). Only one patient, who was receiving placebo, experienced a Grade 4 toxicity, that being ureteral obstruction. None of the differences between arms concerning the percentage of patients experiencing toxicity were clinically or statistically significant. Five percent of toxicities reported in the shark cartilage arm were severe, compared with 6% in the placebo arm.

DISCUSSION

When this study was conceived (initially in 1995), there was considerable enthusiasm concerning the question of whether shark cartilage was an effective anticancer intervention. By the time the study was implemented (in August 2001), however, enthusiasm had waned considerably. This, plus poor patient adherence to the study protocol, as illustrated by noting that only 50% of patients took the shark cartilage for longer than 1 month, resulted in early study closure by an independent NCCTG Patient Safety and Data Monitoring Committee.

The results of this study parallel that reported by Miller and colleagues,[14] both in terms of efficacy as well as the prevalence of patients who did not tolerate the shark cartilage due to gastrointestinal toxicity or who simply did not continue with the study for the prescribed length of time. Since this current study was written and implemented, in vitro and in vivo data have been published on a different form of the same idea, an extract of dogfish cartilage.[33] Properties of this product (AE-941, Aeterna, Toronto, ONT) have been identified to include induction of apoptosis and inhibition of matrix metalloproteinases.[33] Clinical investigations regarding this product have gone from completed Phase I and II clinical trials[33] to a currently ongoing large Phase III trial in patients with lung carcinoma.

This current study did not reach its accrual goals and, therefore, was underpowered for its primary endpoint of median survival. Nonetheless, the fact that patients did not stay on study and that QOL aspects related to well being appeared to be worse for those who received the shark cartilage, there is a lack of enthusiasm regarding further study of the use of this product in powdered form. There is no evidence to suggest a survival benefit from shark cartilage based on our data.

It is conceivable that the observation of shark health and the antiangiogenic properties of cartilage will eventually lead to a form of drug that will have a role in cancer therapy. However, it is prudent to wait until well designed clinical trials are completed, and until we have such evidence, to make recommendations for our patients. For now, it can be summarized that Benefin® shark cartilage did not demonstrate any efficacy in patients with advanced breast or colorectal carcinomas.

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