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Using Quality of Life Measures in a Phase I Clinical Trial of Noni in Patients with Advanced Cancer to Select a Phase II Dose

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Abstract

Purpose—We conducted a Phase I study of noni in patients with advanced cancer. Quality of life measures were examined as an alternate way to select a Phase II dose of this popular dietary supplement.

Patients and Methods—Starting at two capsules twice daily (2 grams), the dose suggested for marketed products, dose levels were escalated by 2 grams daily in cohorts of at least five patients until a maximum tolerated dose was found. Patients completed QLQ-C30 Quality of Life, and the Brief Fatigue Inventory (BFI), questionnaires at baseline and at four week intervals. Scopoletin was measured in blood and urine collected at baseline and at approximately four week intervals.

Results—Fifty-one patients were enrolled at seven dose levels. Seven capsules four times daily (14 grams) was the maximum tolerated dose. No dose limiting toxicity was found but four of eight patients at this level withdrew from the study due to the challenges of ingesting so many capsules. There was a dose response for self reported physical functioning and the control of pain and fatigue. Patients taking four capsules four times daily experienced less fatigue than patients taking lower or higher doses. A relationship between noni dose and blood and urinary scopoletin concentrations was found.

Conclusion—Measuring quality of life to determine a dose for subsequent Phase II testing is feasible. A noni dose of four capsules four times daily (8 grams) is recommended for Phase II testing where controlling fatigue and maintaining physical function is the efficacy of interest. Scopoletin is a measurable noni ingredient for pharmacokinetic studies in patients with cancer.

Background

Noni, extracted from Morinda citifolia or the Indian mulberry plant, is included in the traditional pharmacopoeias of Native Hawaiians, other Pacific Islanders and Asian populations, and has been used to treat various diseases for hundreds of years. Classified as a dietary supplement, it is now commonly taken by cancer patients based on purported usefulness in the disease although there is little scientific evidence to either support or refute these claims. A large marketing enterprise and many different suppliers worldwide promote the food supplement's extraordinary popularity. Furthermore, noni fruit extracts have

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anticancer, antiangiogenic, immunomodulatory and analgesic properties in preclinical models (1–6).

The importance of determining the dose of a dietary supplement that will most likely result in an optimum pharmacologic effect cannot be overemphasized. Many efficacy studies of dietary supplements are conducted without any prior scientific determination of a dose level. Rather a dose that has been traditionally taken or recommended by the marketer of the product is used. A negative result under these circumstances may result in a useful product being unrecognized and discarded or the full usefulness of a product being hidden. Likewise, chemical ingredients that are associated with useful pharmacological properties may never be discovered unless maximum dose levels are sought.

The purpose of this first Phase I study of noni in patients with advanced cancer was to study increasing dose levels of noni above the usual suggested daily dose of 1–2 grams (two-four 500mg capsules) as a first step in addressing the usefulness of noni extracts for cancer patients. Specifically, the study sought to determine either the maximum tolerated or optimal quality of life sustaining dose of capsules containing 500mg of freeze-dried noni fruit extract that would be used in subsequent Phase II efficacy trials. A goal was to determine the feasibility of using symptom relief as a potential marker for dose selection of popular dietary supplements where acute dose limiting toxicity is less likely. Also, the study sought to define toxicities associated with the ingestion of increasing doses of noni and to collect preliminary information on the efficacy of noni in respect to anti-tumor and symptom control properties. In the oncology practice of the first author, several cancer patients troubled by pain and fatigue had reported symptom relief associated with ingesting commercially available noni.

Noni is reported to be composed of over 140 chemical components including novel coumarins, anthraquinones and iridoid glycosides in addition to many commonly occurring flavanoids (7). We had conducted a parallel study in well volunteers to select a bioactive component with putative anticancer activity that enters the systemic circulation after oral intake of noni extract and could be used for product standardization and in pharmacokinetic studies to determine an optimal dosing interval. Of three candidate compounds with putative anticancer activity: scopoletin – a coumarin, asperulosidic acid – an iridoid glycoside and damnacanthol – an anthraquinone; only scopoletin was at detectable concentrations in blood and urine specimens (8). Accordingly, we measured scopoletin in the bloods and urines of subjects at baseline and at each monthly visit to test the feasibility of using it as an indicator of noni gastrointestinal absorption and urinary elimination.

Methods

Subjects

Cancer patients with evidence of progressing disease, for which no standard treatment was available, were the subjects of this study. Patients must have been ambulatory, capable of self care and up and about more than 50% of waking hours (Zubrod Performance Status 0–2) and should have completed all other cancer treatments at least four weeks previously. Through limiting eligibility criteria to performance status of 0–2 Zubrod, patients with

refractory malnourishment and significant organ dysfunction that might significantly confound the absorption, distribution and elimination of noni, were excluded.

If patients were taking medications that are considered by their allopathic practitioner to be essential for their health (e.g. antidiabetic, antihypertensive, lipid lowering), they must have been on these medications at consistent dosing for at least four weeks prior to starting noni. Patients must have agreed to take no other complementary and alternative (CAM) treatments while taking noni. All patients signed informed consent for the study.

Dosing

Subjects were enrolled in the study at seven different dose levels of noni fruit extract as shown in Table 1. Dose level 1 (2 grams per day) was the maximum suggested dose for the marketed product. Capsules containing 500 mg of dehydrated noni fruit were supplied by Innovative Nutriceuticals and Noni Maui.

At least 5 patients were evaluated for a minimum of 28 days at each dose level before entering new patients at the next higher dose level. Additional eligible patients were entered on the same dose levels while waiting for five patients to be on the study for at least 28 days. To maintain consistency, patients were instructed to take capsules on an empty stomach at least one hour before or two hours after food in case food might interfere with the gastrointestinal absorption of noni ingredients.

Measures including quality of life, symptom status

Since much of the anecdotal evidence in support of noni and other CAM treatments relates to cancer patients feeling better after treatment, we explored the feasibility of using quality of life measures in a phase I setting to help select doses of the supplement for subsequent efficacy testing. We added quality of life measures of physical functioning, pain, and fatigue to the usual clinical end points of a phase I cancer study. Patients completed questionnaires at baseline and at approximately four week intervals. Questionnaires used were the QLQ-C30 Quality of Life (including physical functioning, pain, and fatigue components) and the Brief Fatigue Inventory (BFI).

Scopoletin as a marker of noni bioavailability

Urine and blood samples were collected at baseline prior to starting noni, and then every four weeks while patients at the first five dose levels were on study. Urine samples were collected for 12 hours overnight. Concentrations of scopoletin were determined by high performance liquid chromatography (HPLC) with photodiode array (PDA) scanning at 200–700 nm and mass spectrometric (MS) detection. Excretion of scopoletin in urine was determined and reported as the ratio of scopoletin to creatinine levels in each sample (8, 9).

Statistical Analysis

The primary analyses involved testing changes in the quality of life outcome measures over time and across noni dose levels. There were four outcome measures (physical functioning, pain, and two measures of fatigue) and a separate model was run for each. In each model the predictor variables were baseline level of the outcome, noni dose level, and month of

assessment. Because the data included repeated measures, a multilevel (hierarchical) modeling procedure was used for analysis (10–13).

With repeated measures, observations from one person are likely to be more similar than observations across persons. This violates the assumption of independence of observations, which is required when using standard regression procedures. When this assumption is violated, the estimates of the standard errors are likely to be too small, giving biased results. However, through multilevel modeling, the total variance is partitioned into that from the observation (time) level and that from the person level, which addresses the problem of underestimated standard errors.

The results for each of the four models are shown as separate bar charts in Figure 1. All four quality of life outcome measures were scaled to range from 0 to 100, with higher numbers indicating better functioning. In each chart, the vertical axis shows the estimated 60-day change from baseline for the given outcome measure; the horizontal axis shows each of the noni doses. Positive values indicate improvement from baseline, and negative values indicate worsening from baseline. Changes that are statistically different from zero are indicated with an asterisk.

Results

Patient recruitment

Since opening, there was strong interest in the study supported by local print and television media coverage. We received hundreds of enquiries from cancer patients, relatives and friends. Accrual goals were met but at the cost of screening many hundreds of patients for the 51 who met study eligibility criteria.

Many patients were ineligible because their disease was so advanced that they did not meet performance status requirements. Interestingly, a very frequent reason for patients excluding themselves from the study is the requirement that they do not take other CAM treatments. We found that patients without an option for scientifically established effective treatment commonly are unwilling to forego various dietary supplements and other CAM treatments that are often times vigorously promoted by well meaning relatives and friends. These patients declined the study, quite often preferring to add commercially available noni to other CAM they were taking.

Patient characteristics

Fifty-one patients, who met eligibility criteria, enrolled in the study between October 31 2001 and June 30 2006, and started taking the study supplement. Thirty-nine of the 51 patients remained on study for a minimum of 28 days and were evaluable for toxicity, quality of life and the measurement of noni ingredients in blood and urine.

We found no toxicity attributable to noni in twelve patients who elected to withdraw from the study before 28 days and were evaluable for toxicity only. Four of these 12 patients changed their minds wishing to take additional CAM treatments that made them ineligible for the study. Four patients had previously unrecognized rapid cancer progression requiring

hospitalization or inpatient hospice care. Four patients on dose level 7 (28 capsules daily) withdrew from the study before 28 days due to the challenges of ingesting so many capsules on an empty stomach over the day.

Of the 39 patients who were evaluable for toxicity, quality of life, and the measurement of noni ingredients in blood and urine, between five to eight patients were in dose levels 1–6 and dose level 7 contained four patients. The characteristics of the 39 evaluable patients were similar to those usually encountered in a Phase I cancer study where patients have exhausted options for evidenced-based effective treatment The most common disease site was colorectal cancer (9 cases) followed by ovarian cancer (6 cases), lung cancer (4 cases), and pancreatic cancer (3 cases). Twenty-four patients had received prior radiation and 35 patients had received 3 or more prior chemotherapy regimens. Eighteen evaluable patients had a Zubrod Performance Status (PS) of 2, 15 patients had a PS of 1 and 6 patients had a PS of 0.

Distribution of prognostic characteristics across dose levels

The distribution of performance status, extent of disease, and prior treatment did not show any significant variation across the seven dose levels of the study.

Adverse Effects

The main reported adverse effect attributable to noni is queasiness associated with ingesting noni capsules. Patients characterize this as an abdominal discomfort that lasts for several minutes which is different to nausea (feeling like vomiting), and is not associated with vomiting. This occurred in 24% of patients at all dose levels. Two patients also reported Grade 1 nausea. No dose response relationship was apparent.

Maximum tolerated dose

No toxicity related maximum tolerated dose was found with dose escalation to seven capsules four times daily (14 grams daily). However, of the eight patients enrolled at this highest dose level, four patients withdrew from the study before 28 days and three after 28 days due to the challenges of ingesting so many capsules on an empty stomach over the day. Therefore, the dose of seven capsules four times daily (14 grams daily) is considered the maximum tolerated.

Quality of Life, Symptom Status

Of the quality of life measures tested, physical function, pain control and fatigue control (by both CLQ C30 and BFI) showed a trend for improved 60 day maintenance in patients enrolled at the 6–8 gram daily dose levels compared with patients at other dose levels as illustrated in Figure 1. A noni dose of 4 capsules four times daily (8 grams) is recommended for Phase II testing where controlling fatigue and maintaining physical function is the efficacy of interest.

These results suggest that an optimal quality of life sustaining dose focused on maintenance of physical activity and control of fatigue appears to be four capsules four times daily (8 grams daily).

Tumor Response

No measured tumor regression using RECIST criteria were noted in study subjects. However one of three enrolled patients with advanced stomach cancer had no evidence of disease progression for 36 months while taking noni.

Scopoletin as a Marker of Noni Bioavailability

Table 2 shows the concentrations of scopoletin in urines and bloods collected from study patients at the different dosing levels of the study. It demonstrates a statistically significant dose dependent appearance of scopoletin in urine [$F(6,30)=2.7$, $p=.03$] and plasma [$F(6,30)=6.9$, $p<.0001$]. Of note are the higher baseline concentrations of scopoletin for patients enrolled at higher dose levels. An explanation is that with more public awareness as the study progressed, patients at the higher dose levels were ingesting marketed noni supplement at the time of study enrollment.

Discussion

The purpose of this Phase I clinical trial of noni extract was to identify a pharmacologically active dose most likely to work in Phase II placebo controlled efficacy studies. Noni like most popular, commercially available dietary supplements has no identified dose limiting toxicity and the dose suggested by commercial suppliers is not based on scientific rationale. Without using a scientifically determined dose in efficacy studies, the potential usefulness of a dietary supplement or its chemical components may never be discovered. Using a conventional dose escalation design, we found that the maximum tolerated dose was determined not by toxicity but by the quantity of capsules patients were willing to ingest. Furthermore, we found that quality of life measures including physical function and control of fatigue were sustained better in patients taking the mid range dose of 8 gram daily compared with patients taking higher and lower doses and that these differences could not be explained by patient characteristics such as performance status, extent of disease, or prior treatment.

Although the small numbers of subjects and the lack of a placebo controlled setting do not allow any conclusion about the efficacy of noni in patients with advanced cancer, we feel that these findings provide a basis for recommending a dose of four capsules four times daily for subsequent appropriately designed Phase II studies where controlling fatigue and maintaining physical function is the efficacy of interest. This is especially important since we are unable to determine a toxicity-related maximum tolerated dose, the conventional end point for Phase I studies in cancer patients.

No measured tumor regression using RECIST criteria was noted in study subjects. However one patient with advanced stomach cancer had no evidence of disease progression for 36 months while taking noni on the clinical trial. Although this anecdotal case may just reflect the inherent biologic variability of cancer, it is very unusual for advanced stomach cancer to behave this way. Accordingly, stomach cancer should be considered as a target for phase II clinical trials of noni.

Scopoletin was found to be a marker of noni ingestion in patients with advanced cancer. Its utility for product standardization and to address dose and dose interval issues in pharmacokinetic and pharmacodynamic studies should be further studied.

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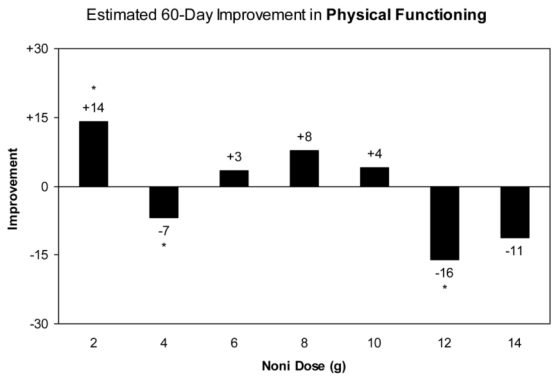

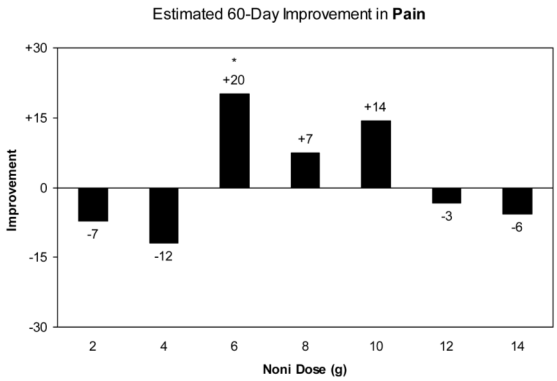

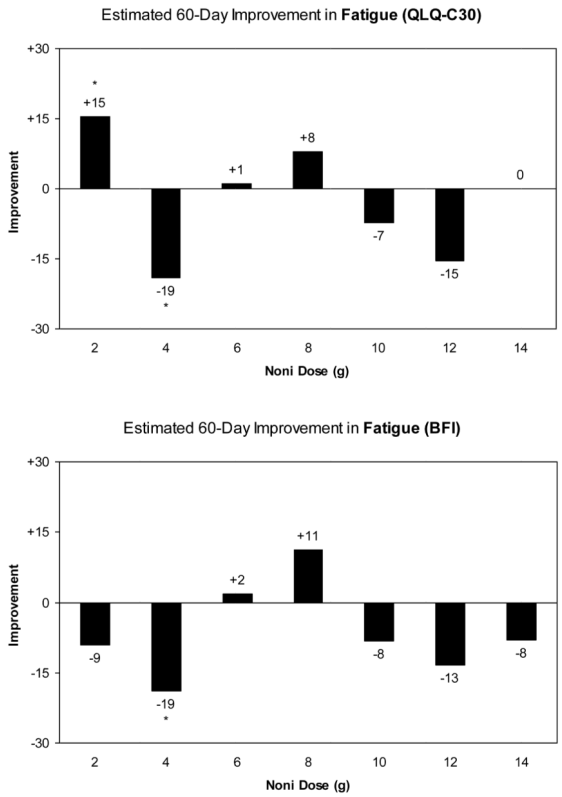

Figure 1.

Note: All estimates are adjusted for baseline values.

* Significantly different from zero (α= .05)

Table 1

Level	Capsules per Day	Total Daily Dose (g)
1	4	2
2	8	4
3	12	6
4	16	8
5	20	10
6	24	12
7	28	14

Notes. Each capsule contained 500 mg noni fruit extract. Level 1 participants took capsules twice daily. All others took capsules four times daily.

Table 2

Mean urinary excretion rates (nmoles per mg creatinine) and plasma levels (nmoles per liter) of scopoletin in patients receiving different dosage of noni capsules

		Urine (nmol/mg)		plasma (nM/L)	
Dose (g)	**n**	**Baseline**	**One Month**	**Baseline**	**One Month**
2	4	0.4	1.7	0.0	5.0
4	5	1.1	1.7	1.1	3.3
6	5	1.0	2.4	3.6	64.9
8	8	1.4	3.4	0.0	11.7
10	5	1.4	6.4	5.9	52.1
12	6	0.2	11.1	13.8	70.6
14	4	4.9	28.4	42.8	138.1