

Results of a Study to Evaluate the Use of Propax to Reduce Adverse Effects of Chemotherapy

Lisa Colodny, PharmD, Kathy Lynch, RN, Charles Farber, MD,
Steven Papish, MD, Karen Phillips, RN, Myrna Sanchez, MD,
Kim Cooper, RN, Owen Pickus, DO, Dayle Palmer, CRNI,
T. Britton Percy, MD, Masih Farooqui, MD,
Jerome Block, MD

ABSTRACT

Objective: To assess the effectiveness of the dietary supplement Propax' with NT Factor' in reducing chemotherapy-induced fatigue, nausea and vomiting, and other selected clinical side effects associated with chemotherapy.

Methods: Using a crossover placebo-controlled, randomized, double-blinded design, 36 patients with cancer were enrolled in the 12-week pilot study. Simultaneously, an open-label trial of Propax' in 22 other patients with cancer was similarly implemented. Recommended daily dose of the study product was 12 tablets and 3 softgel capsules daily.

Results: The consumption of the recommended daily dosage of the dietary supplement Propax' with NT Factor' resulted in an improvement or no change or worsening in chemotherapy-related side effects of fatigue, nausea, impaired taste, diarrhea, general tiredness, constipation, and insomnia. Other chemotherapy-induced toxicities (mouth sores, skin changes, and decreased appetite) were not similarly benefited and progressively became more severe throughout the progression of the study. These results were assessed by standard Quality of Life (QOL) questionnaires completed by patients and nurses in the offices of oncologists participating in the study.

No reported adverse drug events considered to be severe were reported in the study, and when present most were related to mild non-specific gastrointestinal discomfort.

CONCLUSION

Fatigue is one of the most common complaints in cancer patients. The results of this pilot study, both open-label and double-blinded placebo-crossover in design, indicate that patient perception of benefit with Propax' supplementation to chemotherapy is significant in reducing fatigue and other chemotherapy-induced toxicities. As chemotherapy toxicity is expected to worsen or progress with continued therapy, such improvement or lack of worsening of side effects is an important outcome. The results from the blinded study were very similar to the results from the unblinded study both with regard to patient documentation of their symptoms, and nurses' assessments.

SUMMARY

Propax' with NT Factor' supplementation to standard chemotherapy regimens had beneficial impact on several quality of life parameters with a high degree of patient

acceptance of the supplementation regimen that was also confirmed by nurse observations.

Introduction

Cancer patients frequently encounter numerous adverse reactions associated with the administration of chemotherapy. Fatigue is one of the most common complaints.¹⁻⁵ Though common, it is not well understood, and there are numerous theories regarding its severity and prevalence during a patient's daily routine.⁶ While over 75% of cancer patients reported that fatigue adversely affected their lives, only 32% of oncologists recognized this symptom in their patients.⁶ Of more importance, both patients and physicians reported fatigue to be a more prominent adverse event than pain. This is especially interesting given that 74% of patients believed fatigue was untreatable and must simply be endured.⁶ Depending on the chemotherapeutic regimen chosen, the degree of fatigue reported by patients varies widely, from mild² to severe.⁴ It is not surprising then, that Buckingham et al. reported fatigue as the most common and troublesome side effect in ovarian cancer patients who received carboplatin for treatment.⁷ Similarly, fatigue was reported as a significant toxicity in 33% of patients treated with docetaxel for pancreatic cancer.¹ Cancer cachexia, a paraneoplastic syndrome due often to cytokine liberation, is also associated with increasing fatigue.⁸

The difference among cancer types that affect the level of fatigue in patients with cancer has not been formally recognized. However, based on the results of a quality of life survey in 1997, Pater et al. concluded that those patients with metastatic disease and those with poor performance status were more likely to experience fatigue, while older patients and female patients with breast cancer reported less fatigue, as did those whose gastrointestinal responses were controlled by antiemetics; patients with ovarian and lung cancer experienced greater degrees of fatigue.⁹ Modulating fatigue is the level of anemia, commonly present as a result of chronic disease, and secondary to bleeding due to cancer and/or chemotherapy and secondary to radiation injury to the bone marrow.

Nausea and vomiting are also common complaints of oncology patients who receive chemotherapeutic agents.¹⁰⁻¹⁵ Depending on the regimen, the degree of nausea and emesis reported may vary, ranging from mild with minimal emetogenic regimens to severe with substantial emetogenic regimens. Although significant progress has been made in developing more effective means of preventing nausea and vomiting induced by chemotherapy, incomplete or uncontrolled emesis remains a problem for a significant percentage of cancer patients.^{10,16}

Chemotherapy-induced vomiting may actually be classified into acute and delayed phases. The acute phase includes emesis up to 24 hours after chemotherapy is completed; the delayed phase is emesis anytime thereafter.¹¹ While newer agents such as the 5H3 receptor antagonists (ondanesetron, granisetron, and dolasetron) are very effective in controlling emesis during the acute phase, they are less effective during the delayed phase.¹¹

The mechanism of chemotherapy-induced nausea and vomiting is not completely understood. However, interaction between chemotherapeutic agents and the nausea trigger zone has been implicated as a probable cause.¹⁷ Other proposed mechanisms

may be related to tumor metabolism itself, the metabolic response of the body to cytokine release, as well as to surgery, chemotherapy, or radiation.¹⁸

In addition, several risk factors may predispose a patient to chemotherapy-induced nausea and vomiting. Risk factors include being female, being between the ages of 6 and 50 years, and being someone who drinks little or no alcohol.²⁰ Regardless of etiology, chemotherapy-induced nausea and vomiting remain the most feared side effects of many chemotherapy regimens.¹² All chemotherapy-related toxicities directly and indirectly affect the nutritional health of the oncology patient. As a consequence, malnutrition is a common complication that significantly affects both quality of life and survival.²¹

Nutritional improvement for the oncology patient may inhibit deterioration, improve nutritional and immunological parameters, and may help avoid complications.²¹ The protective effects of fat-soluble and other natural antioxidants are well known.⁸ These antioxidant defenses are important in determining immune cell integrity and the functionality of membrane lipids, cellular proteins, and nucleic acids. Additionally, antioxidants are believed to control signal transduction and gene expression in immune cells.⁹ There are several stages where antioxidants may control the progression and malignancy of disease. Antioxidants may also provide protection even when cancer-infected viral activity is present.¹⁸ Dietary introduction of these nutrients may stimulate host immunological defenses and damage malignant cells directly by cycling with consequent oxygen radical production.

The unique dietary supplement, Propax' with NT Factor' (Chart A) was developed to address the nutritional concerns of oncology patients. The formulation is a nutrient tablet base supported by a broad range of vitamins, minerals and micronutrients. NT Factor' is a proprietary nutrient complex designed to maintain normal cell function. In an animal study conducted on NT Factor' at the Henry Ford Health System, it was shown that rats fed a diet containing NT Factor' showed a 20% improvement in mitochondria function over those animals fed the identical diet without NT Factor™, as measured by the Rhodmine flow cytometry.¹⁹ NT Factor™ is comprised of growth factors and specific foods of bifido and lactal species bacterium to promote and maintain a healthy gut and support nutrient absorption. It also contains a specific fraction of phosphoglycolipids extracted from soy that provides an exogenous supply of polyunsaturated phosphatidylcholine(PPC). PPC may function importantly in the repair and maintenance of the cell membrane, a fundamental requirement for normal cell function.

The properties of Propax' and NT Factor' may be of benefit in treating the fatigue and malaise commonly seen in patients with immunosuppressive diseases. This is supported by the recent work of Lilleby et al. who focused on the importance of overall well-being of patients. In fact, quality of life issues such as physical and emotional function and fatigue were of greater significance to the patient than other issues like sexuality or probability of infection.²⁷ Lovely and colleagues concluded similar results by reporting an inverse relationship between quality of life and fatigue.²⁸

Regardless of underlying causes of the nutritional imbalance commonly observed in oncology patients, impact on a patient's quality of life and survival has been extensively analyzed.^{18,29} Celaya et al. reported that the cancer itself might negatively affect nutrition through tumor metabolism and metabolic responses of the body to

cytokine release.²¹ The nutritional status of the patient may already be impaired long before the onset of radiation or chemotherapy.³⁰ Therefore, effective nutritional support may be beneficial in this group of patients reflected in enhanced wound healing, augmented visceral function, and improved cellular immunity.³¹ This is supported by Chuntrasakul et al. who reported significant improvement in nutritional and immunologic parameters in immunocompromised patients who received supplementation with arginine, glutamine, and omega-fatty acids.³² Similarly, Henquin concluded that the health of patients with poor nutritional status during chemotherapy deteriorated, while patients with good nutritional profiles maintained good clinical status.³³ Therefore, prevention or reduction of nutritional deficiencies by adequate therapies may contribute to a reduction in morbidity and mortality in this population.³⁴

Given the negative repercussions of nausea and vomiting, fatigue, compromised nutritional status, and other chemotherapy-related toxicities, agents that decrease these presentations by maintaining normal cell lines on an adequate and fully functioning level will improve the quality of life for the cancer patient. Towards that end this pilot study of the nutraceutical supplement Propax' with NT Factor™ was launched to investigate its potential efficacious effects in chemotherapy-induced fatigue, nausea and vomiting, and other clinical toxic side effects.

Objective

The primary objective of this pilot study, both open-label and double-blinded, was to assess the effectiveness of Propax' with NT Factor™, administered before and during a 12-week regimen of standard chemotherapy for advanced cancer, on the symptoms and side effects of drug toxicity. Efficacy was evaluated via standard instruments that measure quality of life. The secondary objective was to compare the results between a placebo-controlled blinded study and the open-label study to evaluate if the study results are impacted by the trial design.

Data Collection

Data was collected for both the blinded and open-label studies by a designated nurse in each oncologist's office.

As patients entered the study, nurses established baseline information about their symptoms and perceptions of quality of life (QOL) issues via a Nurse Review Questionnaire. The same questions were asked and answers recorded at the time of each chemotherapy administration.

Patients completed a Patient Wellness Questionnaire when they first entered the study, and were asked to complete this QOL questionnaire each week during the study. The patients were given stamped, self-addressed envelopes to return the questionnaires to the physician's office, or they could return them in person on a weekly basis.

Study Design

The unblinded study was an open-label application of Propax', Nutritional Therapeutics, Inc., Hauppague, New York. Patients were placed on nutritional

supplementation 5 to 7 days prior to chemotherapy treatments and continued throughout the first 3 months of chemotherapy treatment. The unblinded study obtained Human Use Committee approval and each patient completed an informed consent form prior to entry into the study.

The blinded study was a double-blind, placebo-crossover trial also requiring Human Use Committee approval and informed consent for patient entry. Patients were randomized to either a placebo or supplement 5 to 7 days prior to the initiation of chemotherapy. After 6 weeks of chemotherapy, patients were then crossed over to the other product (ie, placebo to Propax', or Propax' to placebo). Questionnaires were then evaluated based on improvement or worsening of symptoms from chemotherapy-induced toxicities including fatigue and other QOL issues.

Study Population

Patients for both studies were selected from outpatient chemotherapy centers in California, Florida, Maine, Massachusetts, New Jersey, and New York, for patients with colon, rectal, or pancreatic cancers with identical 5-FU/Leukovorin regimens. Patients with advanced unresectable non-small cell or small cell lung cancer not receiving radiation were also eligible as long as carboplatin and etoposide were used for treatment. The initial study protocol was amended to include patients with sarcoma, breast, ovarian, or other cancers as long as a 3-month survival period was anticipated.

Inclusion / Exclusion Criteria

Patients were excluded from both the blinded and open-label study when they were less than 21 years of age, women of childbearing age, mentally incompetent, or renally impaired (SCr > 2.0 mg/dL). Patients were also excluded when serum bilirubin was 2.0 mg/dl or greater, when weight loss greater than 15% of normal body weight had occurred within the last 4 months, or when the patient spent more than 50% of waking time in bed. All patients concurrently consuming vitamin or nutritional supplements were also excluded.

Patients were eligible for study entry with pathologically-confirmed diagnosis of cancer, appropriate informed consent, and absence of requirement for radiation treatment. No patients in the blinded or unblinded study received radiation therapy during the course of the study. Standard measures for management of chemotherapy clinical toxicities (antiemetics, growth factors, fluids, etc.) were permitted with a physician's order.

Methodology

The dose of Propax' was 1 packet administered 3 times a day. Each packet contains 4 tablets and 1 softgel capsule. The vitamin and mineral supplements (tablets) were administered simultaneously and with food to limit potential gastrointestinal upset. The softgel capsule containing essential fatty acids (EFA) was taken 30 minutes to 1 hour after the tablets to avoid interference with absorption of the vitamin and mineral-containing supplements.

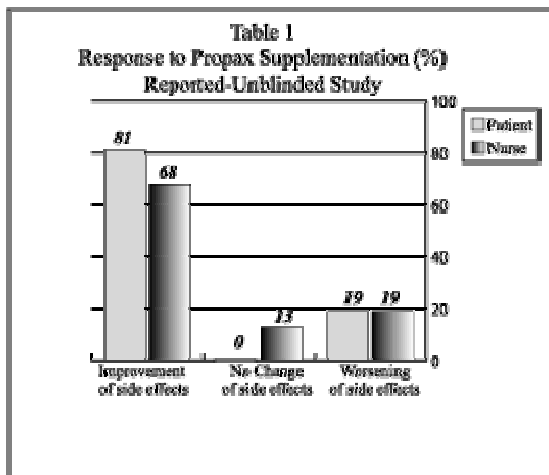
Questionnaires were sorted by study into patient group and nurse group and again by chronological order of administration. Baseline, midpoint, and final values of both patient and nurse questionnaires were documented for all patients for whom at least 3 questionnaires were completed. The data was then evaluated by patient response and criteria response for the efficacy of Propax.' Patients graded wellness from 0 to 4 based on the length of time specific quality of life indicators were adversely affected by chemotherapy (0 = unaffected, 1 = affected part of the time, 2 = affected half of the time, 3 = affected most of the time, and 4 = affected all the time). Nurses graded quality of life indicators on a scale from 0 (unaffected) to 4 (severely effected).

Results of Unblinded Study

Thirty-six patients completed informed consent forms. Of these 36, 22 were enrolled into the unblinded trial with 16 completing the study with at least 3 completed nurse questionnaires to compare baseline and final QOL indicators. The reasons given by patients who initially consented and then chose to not participate in the study were (1) a worsening of their disease, (2) failure to begin chemotherapy, and (3) a general feeling that they could not take the suggested daily dosage of the study product. Patient identification numbers were assigned by the study evaluator to preserve patient confidentiality, and have no impact on study design or methodology. For the 16 patients who completed the study, baseline severity scores were compared to final severity scores assigned by both patient and nurse. Since a grade of 4 was considered severe and 0 was considered less severe, a shift towards the lower (or a negative) number implies improvement in a QOL indicator; a shift towards the higher (or positive) number would indicate a worsening of the criteria. Patients receiving Propax' indicated an improvement in episodes of nausea, diarrhea, constipation, mouth sores, skin changes, and raw mouth/throat. Patients reported significant improvements (> 0.5 change in score) in fatigue, sense of taste, tiredness, insomnia, and overall side effects of chemotherapy. Conversely, worsening of scores was documented by the patients for feeling sad and sick. Patients reported no changes (either improvement or worsening) in the occurrence of throat sores. Nurses reported no change in episodes of diarrhea, worsening of muscle weakness, and vomiting, and noted improvements in appetite (nausea), confusion, constipation, dermatotoxicity (rashes), insomnia, stomatitis, and thrush.

Of the patient questionnaires in the open-label arm of the study, 81% of the patients reported overall improvement in quality of life indicators, and 19% reported a worsening of side effects related to chemotherapy toxicity. Nurses reported that 68% of the patients experienced decreased chemotherapy-induced toxicity, 13% experienced no worsening of these side effects when Propax' was administered, and 19% experienced increased toxicity. (Table 1)

While there was a 13% difference in the patient reporting and nurses reporting on overall improvement, the nurses noted that there was improvement or no worsening of side effects in 81% of the patients completing the open-label study. The nurses and patients both reported the same percentage of worsening of side effects related to chemotherapy treatment (19%).



Results of Blinded Study

Of the 39 patients who initially completed informed consent forms, 3 choose to not enter the study for various reasons: (1) decision to withdraw from chemotherapy treatment, (2) required daily dosage of supplements was too great, and (3) the patient condition worsened prior to entering the study. Of the 36 patients who entered the study, 22 completed treatment and 14 dropped out prior to completion.

Patients who began on Propax' and crossed over to placebo (Table 2)

For patients who began on Propax' and ended on placebo, 9 patients (64%) reported improvement in chemotherapy-related side effects, 2 (14%) reported no change or worsening of side effects, and 3 (21%) reported a worsening of side effects at study conclusion. As reported by patients, the side effects that showed improvement or did not worsen after beginning chemotherapy included fatigue, nausea, impaired taste, diarrhea, general tiredness, constipation, and insomnia. Other chemotherapy-induced toxicities (mouth sores, skin changes, and decreased appetite) became more severe throughout the progression of the study, in contrast to the previously-noted toxicity parameters.

Nurses reported similar results: 7 patients (50%) experienced overall improvement, 4 patients (29%) encountered no overall worsening of side effects with supplementation, and 3 (21%) suffered a worsening of side effects.

Patients who began on placebo and crossed over to Propax'

Patients in the blinded group who began on placebo were crossed over to Propax' after week 6 of the study. At the end of the 12-week study, following crossover to Propax', patients reported improvements in nausea, impaired taste, tiredness, appetite, sick feeling, and sad feeling.

The group of patients who were randomized to initial placebo use began the study with a collective baseline score of 44. This increased to 51 (indicating a worsening of toxicity symptoms) up to the midpoint of the study, resulting in a net mean score increase of .875 points per patient while on placebo. When crossed over to Propax',

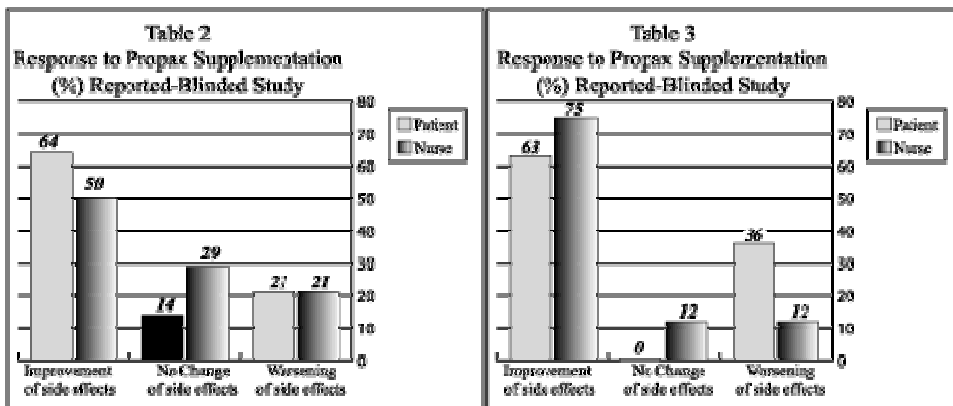
the patients reported a collective 10 point decrease in their toxicity scores, or a net mean change of -1.25 points per patient, which indicates positive improvement of toxicity symptoms following the crossover to Propax' from placebo.

At the conclusion of the study of those patients who began on placebo, 5 patients (63%) reported an improvement in chemotherapy-related side effects after switching to Propax' and 3 patients (36%) reported a worsening of side effects.

The nurses reported several findings for patients who began on placebo. Patients had a group score at the beginning of the study of 29. At midpoint of the study, the group score in this arm of the study decreased 21% to 23, or a net mean change of -.75 points per patient. This would indicate an improvement in toxicities related to treatment for those patients who began on placebo prior to crossover to Propax'. However, following crossover from placebo to Propax', the patients group score decreased 35% to 15 indicating a greater decrease in chemotherapy-related side effects following crossover to Propax'. Following crossover to Propax', the net mean change was -1.0 perpatient as compared to -.75 per patient while on placebo.

The nurses reported that at the end of the study 6 patients (75%) in this arm of the study showed a decrease in side effects, 1 patient (12%) had no change or worsening of side effects, and 1 patient (12%) experienced a worsening of side effects related to treatment at the end of the study.

In summary, results reported by patients and nurses indicated benefit from the Propax' and placebo arms in the blinded study. As reported above, the patients initially randomized to placebo showed a greater improvement in quality of life indicators following the crossover at week 6 of the study to Propax'.



DropOuts

Unblinded arm of study:

Six patients (27%) of the 22 randomized into the unblinded study dropped out before study completion citing as reasons the nausea, abdominal cramps, difficulty swallowing pills, and constipation, though none were reported to be severe. In most cases, the overall medical condition of these patients worsened, and it was not always possible to determine if the symptoms for withdrawal were the result of the study product or expected side effects of the chemotherapy and the disease itself.

Blinded arm of study:

Of the 39 patients who initially signed informed consent forms, 14 patients (36 %) dropped out of the blinded study. An additional 3 patients (8%) who initially consented chose not to enter the study due to a worsening of their condition. Reasons given for withdrawing from the study were: GI discomfort (1), nausea (3), stopped chemotherapy treatments (2), depression or worsening of disease condition (2), admitted into hospice (1), no reason provided (2), difficulty in swallowing pills (2), and constipation (1).

Adverse drug reactions

During the unblinded study, 4 patients experienced adverse drug reactions (ADR). Most were gastrointestinal in nature and included GI discomfort, soft stool, constipation, and flatulence. Other reported reactions included fatigue, difficulty in swallowing, dry skin, runny eyes, insomnia, and peripheral edema. It was difficult to determine if these reactions were related to the study product or events related to the chemotherapy treatments. None were considered severe or warranted withdrawal from study.

During the blinded study, 4 patients in the group that began on placebo reported ADR events. Of those patients who began on Propax', 11 reported an adverse drug reaction. The ADRs reported by patients included GI discomfort, rash, nausea, indigestion, increased bowel movement, sore throat, unpleasant taste in mouth, headache, diarrhea, and dry skin. The majority of the adverse events were related to GI upset, and none were considered severe or warranted withdrawal from study. For those patients who experienced GI upset, they were advised to cut back on the dosage of the study product to one packet of the tablets daily for 3 days, and then titrate the dosage over the next four days, increasing the dosage daily until they were back at the suggested daily dosage of three (3) packets. This procedure worked for those who complained initially of GI upset, and following this procedure there were no further complaints of GI upset by those patients who remained in the study. For those who complained of unpleasant taste in their mouth, this was determined to be related to the clear gel capsule (EFA) which has a fishy taste as described by some patients. Nurses reported that they could not attribute each adverse event to the study product as some complaints may have been related to the chemotherapy treatment.

Concomitant medications

In addition to standard chemotherapeutic protocols that included 5-FU/Leukovorin regimens, carboplatin, and etoposide, patients also received Medrol dosepack, compazine, acetaminophen, and Ibuprofen as prescribed by their physician for clinically-vindicated conditions. These medications can cause GI upset and may induce weakness as well. One patient in each study documented the use of filgrastim, a granulocyte-stimulating factor.

Discussion

Many factors can influence the nutritional status of cancer patients, including cachexia, nausea, vomiting, decreased caloric intake, or the specific choice of oncology therapies.²³ Although the influence of these factors on nutrition is not well

defined, the relationship has been extensively studied. Tonosaki et al. reported skinfold thickness as a nutritional indicator was significantly influenced by nausea and vomiting and also by infectious processes associated with elevated temperatures.²⁴ Similarly, Sarna et al. reported a parallel relationship between decreased calorie consumption and functional status in lung cancer patients over a 6-month period.²⁵ In both the blinded and open-label arms of this study, both patients and nurses reported improved quality of life scores for appetite changes and nausea. Improved appetite and decreased nausea may positively affect quality of life by nutritionally optimizing the gastrointestinal conditions and decreasing the body's response to chemotherapy-induced toxicities. This is consistent with the work of Grunberg et al. who proposed that decreased episodes of nausea/vomiting will result in a significant improvement in quality of life indicators. Additionally, the correlation between decreased nausea and decreased cost for total care has been documented.²⁶

The results of this pilot study, both open-label and double-blinded placebo-crossover in design, indicate that patient perception of benefit with Propax' supplementation to chemotherapy is significant. Benefit was seen predominantly in nausea, fatigue, and diarrhea. The improvements warrant further study as most oncology patients report persistent fatigue,³⁵ nausea,³⁶ dry mouth,²² and taste changes^{22,37} throughout treatment modalities. As chemotherapy toxicity is expected to worsen or progress with continued therapy,²² such improvement or lack of side effects worsening is an important outcome.

It is interesting to note that the results from the blinded study were very similar to the results from the unblinded study. Patients in the unblinded arm reported an 81% improvement in quality of life indicators and 19% reported a worsening of side effects related to chemotherapy toxicity. At the conclusion of the blinded arm, 64% of the patients who began on Propax' reported an improvement in quality of life indicators and decrease in chemotherapy-related side effects, 14% reported no change or worsening of side effects, and 21% reported a worsening of quality of life indicators at study conclusion. Of those patients who began on Propax' and crossed over to placebo, 63% reported an improvement in quality of life indicators and a decrease in chemotherapy-related side effects, and 36% reported a worsening of side effects. Three (3) patients who were crossed over to placebo after beginning on Propax' requested to return to the original product after reporting a worsening of their side effects following crossover.

These patient-reported results were supported by nurse reports. At the end of the unblinded study, nurses reported that 75% of the patients showed an increase in quality of life indicators and a decrease in side effects related to chemotherapy treatment, 12% of the patients had no change or worsening in quality of life indicators and side effects, and 12% of the patients experienced a worsening of side effects related to their treatment.

In the blinded study, nurses reported that for those patients who began on placebo and crossed over to Propax' 75% experienced an improvement in quality of life indicators and a decrease in chemotherapy-related side effects, 12% had no change in quality of life indicators nor worsening of side effects, and 12% reported a worsening of side effects. For those patients who began on Propax' and crossed over to placebo, nurses reported that 64% reported an improvement in quality of life indicators and decrease in side effects, 14% reported no change nor worsening of

side effects, and 21% reported a decrease in quality of life indicators and an increase in side effects related to chemotherapy.

While it was initially anticipated that a larger percentage of patients might experience a decrease in quality of life indicators and increase in side effects following crossover from Propax' to placebo, one possible explanation may be that the duration of the study and the rapid crossover design may not have permitted adequate separation from the Propax' effects from any subsequent placebo effects. The duration of any Propax' effects after discontinuation is not known nor addressed in this study.

Although this initial pilot study involved small numbers of patients, the results of the study were confirmed in both the open-label and double-blinded, placebo-controlled arms of the trial. Benson et al. noted in their study that there was little evidence that estimates of treatment effects in observational studies published after 1984 were either consistently larger than or qualitatively different from those obtained in randomized, controlled trials.³⁸

Concato et al. also reached the same conclusion in a recent study.³⁹ After looking at randomized controlled trials, observational studies, and the hierarchy of research designs published in five major medical journals from 1991 to 1995, Concato et al. concluded that the results of well-designed observational studies (with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic.

CONCLUSIONS

Based on the results of this initial pilot study, additional well-designed clinical studies with larger patient populations are justified and encouraged in order to draw further conclusions on the effectiveness of nutritional supplements like Propax' in cancer treatment. This initial pilot study provides evidence that the use of a nutritional supplement such as Propax' may correlate with positive results for decreased fatigue, vomiting, nausea, and diarrhea, as well as with an improvement in overall well-being; effects such as mucositis, skin toxicity, and appetite were not similarly noted. Larger studied numbers of patients are required to obtain firm statistical support for these noted early encouraging findings. Future studies with a larger patient population will also help determine if a dose reduction of chemotherapy can be avoided with the use of a nutritional supplement such as Propax', which could permit toleration of higher levels of drug therapy. The cost-effectiveness of such strategies should also be evaluated relative to decreasing treatment costs by avoiding episodes of neutropenia, sepsis, emesis, and other chemotherapy-induced side effects.

The dropout rates in the blinded study appeared more related to the number of pills required for adequate dosage and a worsening of the actual cancer itself rather than to any direct Propax' side effects.

In summary, Propax' supplementation to standard chemotherapy regimens had beneficial impact on several quality of life parameters with a high degree of patient acceptance of the supplementation regimen.

ACKNOWLEDGEMENT

This study was supported in part by an unrestricted educational grant from Nutritional Therapeutics, Inc. of Hauppauge, New York. The editorial assistance of Allen Montgomery, RPh, and Steve Evans, MS, is acknowledged.

References

1. Okada S, Sakata Y, Matsuno S, et al. Phase III study of docetaxel in patients with metastatic pancreatic cancer: a Japanese cooperative study. Cooperative Group of Docetaxel for Pancreatic Cancer in Japan. *Br J Cancer*. 1999 May;80(3-4):438-43.
2. Herben V, Panday V, Richel D, et al. Phase I and pharmacologic study of the combination of paclitaxel, cisplatin, and topotecan administered intravenously every 21 days as first-line therapy in patients with advanced ovarian cancer. *J Clin Oncol*. 1999 Mar;17(3):747-55.
3. Noda K, Tanaka K, Ozaki M, et al. Early phase II trial of oral etoposide administered for 21 consecutive days in patients with cervical or ovarian cancer. ETP 21 Study Group Cervical-Ovarian Cancer Group. *Gan To Kagaku Ryoho*. 1998 Nov;25(13):2061-8.
4. Zamagni C, Martoni A, Cacciari N, et al. The combination of paclitaxel and carboplatin as first-line chemotherapy in patients with stage III and stage IV ovarian cancer: a phase I-II study. *Am J Clin Oncol*. 1998 Oct;21(5):491-7.
5. Mross K, Hauns B, Haring B, et al. Clinical phase I study with one-hour paclitaxel infusion. *Ann Oncol*. 1998 May;9(5):569-72.
6. Vogelzang N, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. *Semin Hematol*. 1997 Jul; 34 (3 suppl 2): 4 -12.
7. Buckingham R, Fitt J, Sitzia J. Patients experiences of chemotherapy: side-effects of carboplatin in the treatment of carcinoma of the ovary. *Eur J Cancer Care*. (Engl) 1997 Mar;6(1):59-71
8. Mantovani G, Maccio A, Lai P, et al. Cytokine involvement in cancer anorexia / cachexia: role of megestrol acetate and medroxyprogesterone acetate on cytokine downregulation and improvement of clinical symptoms. *Crit Rev Oncog*. 1998; 9(2): 99-106.
9. Bergelson L, Dyatlovitskaya E, Sorokina I, et al. Phospholipid composition of mitochondria and microsomes from regenerating rat liver and hepatomas of different growth rate. *Biochim Biophys Acta*. 1974. Sep 19;360:361-5.
10. Rizk A, Hesketh P. Antiemetics for cancer chemotherapy-induced nausea and vomiting. A review in development. *Drugs R D*.1999 Oct;2(4):229-35.
11. Tavorath R, Hesketh P. Drug treatment of chemotherapy-induced delayed emesis. *Drugs*. 1996 Nov;52(5):639 - 48.

12. Perez E, Gandara D. Advances in the control of chemotherapy-induced emesis. *Ann Oncol.* 1992 Aug; 3 suppl 3: 47-50.
13. Hesketh P. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT₃ receptor antagonists. *Support Care Cancer.* 1994 Sep; 2(5): 286-92.
14. Del Favero A, Roila F, Tonato M. Reducing chemotherapy-induced nausea and vomiting. Current perspectives and future possibilities. *Drug Saf.* 1993 Dec; 9(6): 410-28.
15. Pendergrass K. Options in the treatment of chemotherapy-induced emesis. *Cancer Pract.* 1998 Sep-Oct; 6(5): 276-81.
16. Tonato M, Roila F, Del Favero A, et al. Antimetics in cancer chemotherapy: historical perspective and current state of the art. *Support Care Cancer.* 1994 May; 2(3): 150-60.
17. Gralla R. Current issues in the management of nausea and vomiting. *Ann Oncol.* 1993; 4 suppl 3: 3-7.
18. Celaya-Perez S, Valero-Zanuy M. Nutritional management of oncologic patients. *Nutr Hosp.* 1999 May; 14 suppl 2: 43S-52S.
19. Letter from Michael D. Seildman, MD, Department of Otolaryngology Head & Neck Surgery, Henry Ford Medical Center, Detroit, Michigan.
20. Doherty K. Closing the gap in prophylactic antiemetic therapy: patient factors in calculating the emetogenic potential of chemotherapy. *Clin J Oncol Nurs.* 1999 Jul; 3(3): 113-9.
21. Celaya-Perez S, Valero Zanuy MA. Nutritional management of oncologic patients. *Nutr Hosp.* 1999 May; 14 suppl 2: 43S-52C.
22. Lisa M, Siston A, Haraf D, et al. Quality of life and performance in advanced head and neck cancer patients on concomitant chemoradiotherapy: a prospective examination. *J Clin Oncol.* 1999 Mar; 17(3): 1020-8.
23. Mercadante S. Nutrition in cancer patients. *Support Care Cancer.* 1996 Jan; 4(1): 10-20.
24. Tonosaki A, Kazuma K, Ishiguro Y. A study of changes in the nutritional status of patients receiving cancer chemotherapy. *Nihon Kango Kagakkaishi.* 1993 Jul; 13(1): 12-9.
25. Sarna L, Lindsey A, Dean H, et al. Nutritional intake, weight change, symptom distress, and functional status over time in adults with lung cancer. *Oncol Nurs Forum.* 1993 Apr; 20(3): 481-9.
26. Grunberg S, Boutin N, Ireland A, et al. Impact of nausea/vomiting on quality of life as a visual analogue scale-derived utility score. *Support Care Cancer.* 1996 Nov; 4(6): 435-9.

27. Lilleby W, Fossa S, Waehre H, et al. Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. *Int J Radiat Oncol Biol Phys.* 1999 Mar 1; 43(4): 735-43.
28. Lovely MP. Quality of life of brain tumor patients. *Semin Oncol Nurs.* 1998 Feb; 14(1): 73-80.
29. Rivadeneira D, Evoy D, Fahey T, et al. Nutritional support of the cancer patient. *CA Cancer J Clin.* 1998 Mar-Apr; 48(2): 69-80.
30. Fietkau R. Principles of feeding cancer patients via enteral or parenteral nutrition during radiotherapy. *Strahlenther Onkol.* 1998 Nov; 174 (suppl 3): 47-51.
31. Nixon D. The value of parenteral nutrition support: chemotherapy and radiation treatment. *Cancer.* 1986 Oct 15; 58(suppl 8): 1902-3.
32. Chuntrasakul C, Siltharm S, Sarasombath S, et al. Metabolic and immune effects of dietary arginine, glutamine, and omega-3 fatty acids supplementation in immunocompromised patients. *J Med Assoc Thai.* 1998 May; 81(5): 334-43.
33. Henquin N, Havivi E, Reshef A, et al. Nutritional monitoring and counseling for cancer patients during chemotherapy. *Oncology.* 1989; 46(3): 173-7.
34. Pille S, Bohmer D. Options for artificial nutrition of cancer patients. *Strahlenther Onkol.* 1998 Nov; 174 (suppl 30): 52-5.
35. Broeckel J, Jacobsen P, Horton J, et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 1998 May; 16(5): 1689-96.
36. Morrow G, Roscoe J, Hickok J, et al. Initial control of chemotherapy-induced nausea and vomiting in patient quality of life. *Oncology.* 1998 Mar; 12(suppl 4): 32-7.
37. Wickham R, Rehwaldt M, Kefer C, et al. Taste changes experienced by patients receiving chemotherapy. *Oncol Nurs Forum.* 1999 May; 26(4): 697-706.
38. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med.* 2000; 342: 1878-86.
39. Concato J, Shah N, Horwitz R I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000; 342: 1887-92.